ESCMID

ESCMID Postgraduate Education Course

Carbapenemase-producing Gram-negative Microorganisms: Detection, Epidemiology and Therapeutic Challenges

Athens, Greece
1 – 2 December 2011

Case presentations : from the agar plate to the patient

A. Antoniadou & GL Daikos

CASE 1

Male, 50 years old, aplastic anemia
Transferred from a private hospital for hematological treatment
Previously hospitalized for a month and exposed to multiple antibiotics (carbapenems, aminoglycosides, vancomycin, ciprofloxacin)
Pancytopenia (neutropenic)
On day 2 of admission becomes febrile (spiking to 39° C)
He is hemodynamically stable, no signs of site of infection.
He has a CVC (right jugular) with no exit site signs of infection

Blood and urine cultures are taken, a chest X-ray is performed and empiric antimicrobial treatment is initiated

Which would you prefer as initial antimicrobial regimen?

1. Pip/tazo + amikacin
2. Meropenem
3. Meropenem + gentamicin
4. Meropenem + colistin
5. Other

The patient starts treatment with meropenem and colistin

Blood culture is positive on day 2 and on day 3 *K.pneumoniae* (KPC producing) is identified

The patient is still febrile

Amikacin	**> 8**	**R**
Amox/clav	**>16/8**	**R**
Aztreonam	**>16**	**R**
Cefepime	**>16**	**R**
Ceftazidime	**>16**	**R**
Cefuroxime	**>16**	**R**
ciprofloxacin	**>2**	**R**
Colistin	**2**	**S**
Gentamicin	**>8**	**R**
imipenem	**16**	**R**
Meropenem	**4**	**I**
Pip /tazo	**>64/4**	**R**
Tigecycine	**1**	**S**

Would you change treatment?

1. Continue meropenem + colistin
2. Tigecycline monotherapy
3. Meropenem monotherapy
5. Tigecycline + colistin
6. Meropenem + tigecycline
7. Remove CVC

- The patient continued successfully treatment with meropenem (3h infusion) and colistin
- CVC was removed
- The patient was screened and found rectally colonized with the same Klebsiella

Case 2

38-year-old woman presented with a closed head injury. An EVD was inserted on day 1 and removed on day 10. On that day the patient was febrile (38), no other site of infection was evident and the CSF before EVD removal showed elevated WBC (500) and increased albumin. Cultures of blood and CSF were negative

Culture-negative ventriculitis was treated empirically with intravenous vancomycin, meropenem and amikacin

The patient was afebrile but with fluctuating level of consiousness and confusion. Increased intracranial pressure was evident from a new CT scan and a new EVD was inserted on day 20.

CSF taken from the new EVD yielded CP Acinetobacter baumanii sensitive only to colistin and tigecycline

Choices :

1. Colistin IV 3MUX3
2. Colistin IV 9MU initially and 4.5 MU X2 thereafter
3. Colistin IV 9 MU QD
4. Colistin intraventricular 0.5 MU qd
5. Colistin IV + intraventricular
6. Colistin IV+ tigecycline IV + colistin intraventricular

The patient was treated with colistin IV (3MU X3) and intraventricular (0.5 MU qd) for 4 weeks. CSF was sterile after the first week of treatment and the patient on week 3 underwent placement of a ventriculoperitoneal shunt. Clinical recovery occurred and the patient underwent rehabilitation.

Case 3

46 y old woman
AML in remission after a first relapse
Undergoes HSCT
DAY 3 : Neutropenic
DAY 6 : Febrile
No signs of infection, no mucositis
Empiric antimicrobial treatment with pip/tazo + amikacin
Day 7: painful redness along the right thigh. Vancomycin in added

Redness evolves to a huge ecthyma-gangrenosum-like lesion covering the whole right femoral-inguinal area

Day 8: notification from the lab about positive blood cultures with Gram negative The patient is still febrile and treatment changes to meropenem

Day 10: Pseudomonas aeruginosa is identified in blood culture, sensitive only to colistin and gentamicin

What changes to the antimicrobial regimen?

1. Stop vancomycin
2. Colistin monotherapy
3. Colistin + gentamicin
4. Meropenem + gentamicin
5. Meropenem + colistin
6. Meropenem + colistin + gentamicin

The patient was left on Meropenem and colistin + gentamicin was added

CT examination of the femoral –inguinal area showed inflammation spreading along fascia to both thighs, the perineum and the right buttock, but no muscle invasion was noted.

- The patient was in severe pain requiring opioids, spiking high fevers but without hemodynamic instability for the next 9 days.
- On day 14 post transplantation the neutrophil count recovered. Improvement continued until day 34 when surgical debridement was decided (PLT>30,000/mm^3)
- the same multiresistant *P. aeruginosa* strain was again isolated from the drained area.
- Since day 36 and for the next 4 weeks, the patient continued on colistin monotherapy and topical surgical care.
- The wound was left to heal secondarily

CASE 4

Male, 75 years old

- The patient is admitted to a regional hospital due to fever with rigors starting 24 hours earlier. He was found by his son on the flour with loss of consciousness.
- ED: Lethargic, GCS 13, oliguric, tachypneic
- Shock, diarrhoea (3), one episode of gastroplegic vomiting
- Physical examination: no apparent source of sepsis

MEDICAL HISTORY

- Arterial Hypertension (since the age of 40 years)
- 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)]
- Prostate hypertrophy
- Cholocystectomy

INITIAL LABORATORY TESTS

- Hct 40.1, **WBC 21,400** c/mm3 (pmn), 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
- Blood Gas : lactic acidosis. Urine microscopy: no significant findings
- 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%

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
- Extrarenal Dialysis 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

TRANSFER TO THE ICU OF ATTIKON HOSPITAL (DAY 4)

- CNS
  - Lethargic but oriented, obeys orders, no focal neurology
- Respiratory
  - pH 7.32, pO2 146,pCO2 42, HCO3 22, Lac 1.2 (MV 0.6)
    - Tachypneic (30/min), cough with minimal secretions
- Heart
  - Proxysmal Atrial Fibrillation
  - Low dose vasopressors (2-3 γ)
- Abdomen
  - Dilated, diffuse rebound tenderness, sounds absent
  - Anuric, extrarenal dialysis

CLINICAL COURSE (DAY 4-10)

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

- **Patient clinically improving, Afebrile**
  - Respiratory and hemodynamically stable
  - PLT count are gradually recovering
  - Lethargic, occasionally confused
  - Starts dienteric feeding- 1-2 diarrhoeas per day
  - Renal function not improved

- **Repeated testing for *C.difficile*: negative**
- **Lumbar puncture: not significant findings**
- **Surveillance cultures : CPKP in rectum, CP Acinetobacter in bronchial secretions**
- **CPKP R tocarbapenems (MIC>8), gentamicin, Intermediate sensitivity to colistin (MIC=4), Tigecycline (MIC=2)**

INTUBATION (DAY 11)

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

WHICH ARE YOUR NEXT DIAGNOSTIC AND THERAPEUTIC MANOEVRES

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

WHICH IS YOUR EMPIRIC ANTIBIOTIC CHOICE?

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

BLOOD CULTURES: *KLEBSIELLA SPP (KPC PRODUCING)*

Meropenem MIC>16

Gentamicin MIC>8

Colistin MIC>16

Tigecycline MIC 2

WHICH IS YOUR THERAPEUTIC CHOICE NOW?

1. Meropenem +gentamicin
2. Tigecycline 100mg loading followed by 50mgX2
3. Tigecycline double dose
4. Tigecycline +gentamicin
5. Colistin +tigecycine
6. Fosfomycin +tigecycline

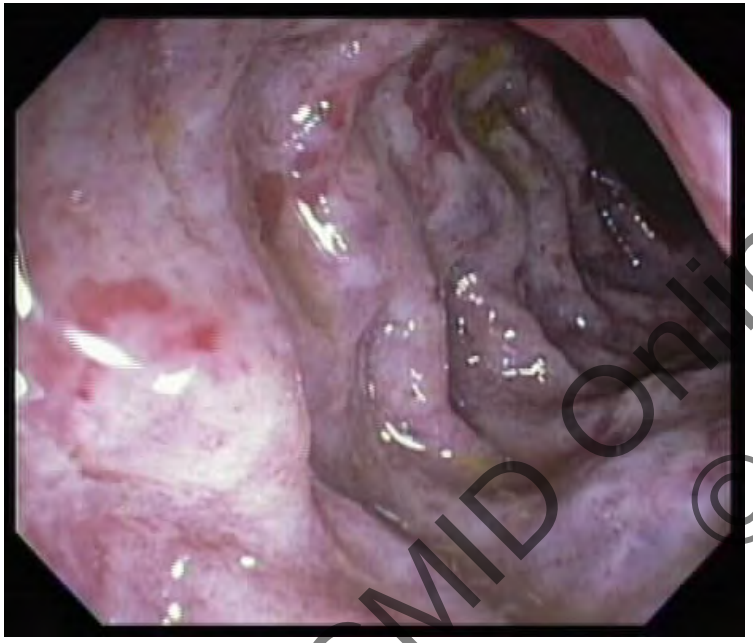
LABORATORY EVALUATION (DAY 11)

- 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

CLINICAL COURSE (DAY 11-18)

- Remains intubated
  - Hemodynamically stable
  - Receives tigecycline 100mgx2+colistin 2MUX3
  - CVVH
  - Diarrhoea (often bloody)

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

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. IC presents either as an occlusive or a non-occlusive form. Many cases are misdiagnosed as suffering from 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
- Bacterial translocation and sepsis has been shown to occur with the loss of mucosal integrity

ISCHEMIC COLITIS INDICATIONS FOR SURGERY

- In the absence of colonic gangrene or perforation, general measures of supportive care are recommended.
- Clinical suspicion of colonic infarction may arise if there are signs of clinical deterioration despite conservative therapy, such as sepsis, persistent fever and leukocytosis…
- About 20% of patients with acute IC will require surgery with an associated mortality rate of up to 60%

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

WHICH COMBINATION WOULD YOU PREFER?

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

BLOOD CULTURE
KLEBSIELLA PNEUMONIAE (CPKP)

Meropenem MIC>16

Gentamicin MIC>8

Colistin MIC>16

Tigecycline MIC 2

WHICH IS YOUR THERAPEUTIC CHOICE NOW?

1. Tigecycline double dose + fosfomycin
2. Colistin + tigecycline + fosfomycin
3. Colectomy
4. Other

YOUR NEXT THOUGHTS

1. Inadequate coverage
2. Possible endocarditis
3. Possible septic thrombophlebitis
4. Continuous ischemia of the bowel-recurrent allothesis
5. Check MIC to fosfomycin

DIAGNOSTICS OF RECURRENT BACTEREMIA

1. Thorax CT scan: moderate right pleural effusion, small atelectasis of the right lower lobe
2. Abdomen CT scan: Colonic aperistalsis, mural thickening more extended than in the previous scan
3. Cardiac Echo-no evidence of endocarditis
4. Tripplex of the veins of the limbs: thrombosis of left femoral vein

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

PATIENT'S COURSE (DAY 20-29)

- Antimicrobials
  - Colistin
  - tigecycline
  - fosfomycin
- Hemodynamically stabilised, BC(-)
- MIC to fosfomycin >1024
- Thrombocytopenia
- Abnormal LFTs

Patient's course (Day 30-39)

Tigecycline is replaced by doripenem due to deterioration of LFTs

Patient stable for a week with improvement of LFTs

Day 38

New febrile episode

New bacteremia with the same Klebsiella

Tigecycline restarted

Gross hemorrhagic stools

Lactic acidosis

Succumbed

Bacteremic

FINAL DIAGNOSIS

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