Difficult to treat- germs or imunocompromised pacient?

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Context actual

- Pacient COVID
- Pacient septic
- Pacient cu encefalita, meningita, osteomielita
- Pacient cu boala eruptiva
- Pacient cu tuse convulsiva
- Pacient cu boala respiratorie, digestive, urinara
- **Pacient imunocompromis:**

  - Diabet zaharat tip I/II
  - patologie oncologica
  - tratament chimioterapic
  - tratament cronic imunosupresor (terapie biologica, cortizon) + status post transplant de organ

Pacientul imunocompromis cu sdr febril:

- **Nu este o cauză pierdută**
- **Nu este o enigmă**
- **Nu este o simplă coincidență**
- **Nu este o eroare de diagnostic**
- **Nu este o situație de rutină**

Cum abordam pacientul nostru?

- Anamneza
- Examen clinic
- Paraclinic
- Tratament

- **Parametri clinici:**
  - qSOFA
- **Parametri biologici:**
  - SOFA
- **Parametri epidemiologici:**
  - Scorul Carmeli ??

QSOFA

- **– tensiunea arterială sistemică ≤ 100 mmHg**
- **– alterarea statusului mental**
- **– frecvența respiratorie ≥ 22 resp/min**

- **AVANTAJE:** Nu necesită explorare paraclinică
  Poate fi utilizat rapid și repetat frecvent
- Ajuta la inițierea sau escaladarea terapiei
  Transfer spre terapie intensivă

SCOR SOFA- limite?

SOFA score	0	1	2	3	4
Respiration PaO_2FIO_2 or SaO_2/FIO_2 mmHg	>400	<400 221-301	<300 142-220	<200 67-141	<100 <67
Coagulation	>150	<150	<100	<50	<20
Liver Birilubin(mg/dl)	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Cardiovascular Hypotension	No hypotension	MAP <70	Dopamine ≤5 or any	Dopamine >5 or notepinephrine ≤0.1	Dopamine >15 or norepinephrine >0.1
CNS (GCS)	15	13-14	10-12	6-9	<6
Renal Creatinine (mg/dl) or urine output (ml/d)	<1.2	1.2-1.9	2.0-3.4	3.5-4.9 or <5.00	>5.0 or <200

SCORUL CARMELI:

Stratificarea riscului de rezistenta la antibiotice

A.Contactul cu sistemul de sanatate:

(1) fara contact prealabil

(2) contact cu asistenta sanitara (internare recenta, rezident sanatoriu, dializa) fara proceduri invazive

(3) spitalizare lunga (>5 zile) si/sau proceduri invazive

B.Tratament antibiotic:

(1) fara tratament

(2) cu tratament

C. Caracteristicile pacientului:

(1) tanar, fara comorbiditati

(2) varstinc, mutiple comorbiditati

(3) Imunodepresii (diabet zaharat, neoplazii, fibroza chistica, SIDA, neutropenie, alte imunodeficiente severe)

Precizarea scorului: se dau mai mare scor (1, 2 sau 3) atat timp cat pacientii A, B sau C

Z.P.

- 14.09 – CRP 7.84, Troponina T 135.6
- 17.09 – CRP 5.08

19.09 – STOP Metronidazol

- 23.09 – CRP 5.08, Troponina T 96.63
- 28.09 – CRP 10.58, MF Clostridioides difficile – GDH prezent

Tratament: remaniere cu Ertapenem (5 zile) + Fluconazol+Biseptol si Aciclovir (luni, miercuri, vineri)+Vancomicina po

- 01.10 – CRP 8.04, WBC 2150/mm3, trombocite 128000/mm3

04.10 – STOP Fluconazol

- 06.10 – CRP 7.56

Tratament: remaniere Meropenem + Metronidazol + Targocid (Teicoplanin)

THE PATIENT...ZP

- Sex masculin, 60 ani
- Data internarii 10.09.2024

- Motivele internarii: febra,
  frisoane, inapetenta
  stare generala grava, hipotensiune arteriala

ZP- APP

- LMNH difuz cu celula mare B
- Chimioterapie recenta august 2024
- Ileostoma in martie 2024-
- plastron tumoral abcedat aprilie 2024
- Hepatita cronica cu VHC
- Insuficienta mitrala minora
- Sdr hipoanabolic
- Sepsis urinar in aug 2024- germ neidentificat

PARACLINIC

Z1

Z1

Z3

LEUCOPENIE

NEUTROPENIE SEVERA

SDR INFLAMATOR

CT 10.09.2024

- Regresia formatiunilor nodulare adiacente polului posterior al rinichiului stang cu dimensiuni de 6,3 respectiv 4,5 cm Persistenta unui aspect , aglutinat " al anselor intenstinale in usoara regresie comparativ cu examinarea anterioara .(plastron ?) . Este dificil de exclus o eventuala colectie in conditiile unei examinari native .

CT 26.09.2024

- Trunchi de artera pulmonara, artere pulmonare principale, lobare si segmentare- omogen opacifiate.
- Hemidiafragm stang moderat ascensionat, asociind mica arie de atelectazie subpleurala, laterobazala.
- Emfizem paraseptal apical bilateral si paracardiac LSS (moderat).
- Cativa ganglioni mediastinali si hilar pulmonar bilateral fara aspect patologic.
- Lama de pericardita versanti infero-laterali (maxim 11 mm dreapta).
- Fara epansamente fluide pleurale.

CT abdominal 11.10.2024

- CONCLUZII:
- Voluminoasa formatiune expansiva in FID mezogastru si hipogastru cu invazie intestinala si inglobarea pachetului vascular iliac extern dret, cu extravazare de substanta de contrast intratumorala (sangerare

intratumorala), cel mai proabil in contextul ruperii vasculare intratumorale.

- Formatiune expansiva in spatiul perirenal stang.
- Tromboza vena iliaca externa si VFC dreapta.
- ADP abdominale.

- HC Proteus Mirabilis MDR (S- Amikacin, Meropenem, Ertapenem) – Meropenem+ Amikacin+ Fluconazol (16 zile)+ Metronidazol
- Febril in a16a zi- Ertapenem, HC + Toxina Clostridium POZ ---+ Vancomicina Pos
- Sub support de NA 24 zile ritm 5 ml/ora---0,5-1ml/ora
- Z20 HC POZITIVA Proteus mirabilis- aceeasi sensibilitate

Evolutie

- Consult cardiologic in dinamica- fara imagini de aditie valvulara
- Consult hematologic - Accufil pana la Neutrofile>1000/mmc,
  - ATB terapie cu spectru larg,
  - MER
- Consult Chirurgical- recomandare de interventie chirurgicala si transfer in sectia de Chirurgie- pacientul Refuza
- Consult si consiliere psihologica
- Externare la cerere 16.10.2024

T. 55 ani

- LITIAZA RENALA
- ITU RECIDIVANTA

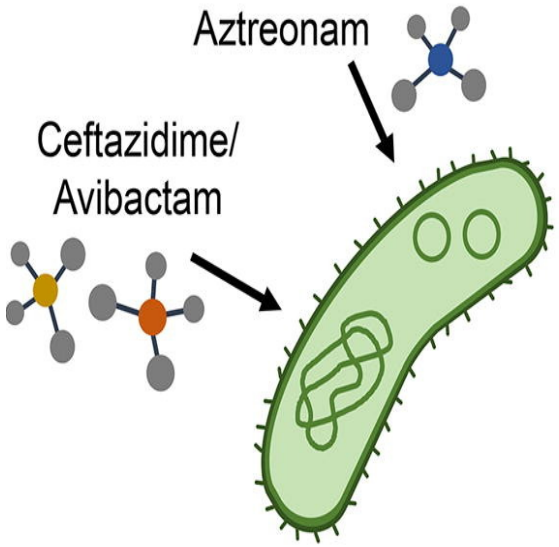
- KLEBSIELLA PNEUMONIAE MDR (urocultura)
- Hemoculturi – negative
- La internare (17.06) CRP 13.9, WBC 18270/mm3, neut 15.27
  (22.06) CRP 0.92
  (26.06) CRP 1.4

Antibiotic – Zavicefta (Ceftazidim-Avibactam)+ Aztreonam

TM- ITU cu Klebsiella Pneumoniae XDR

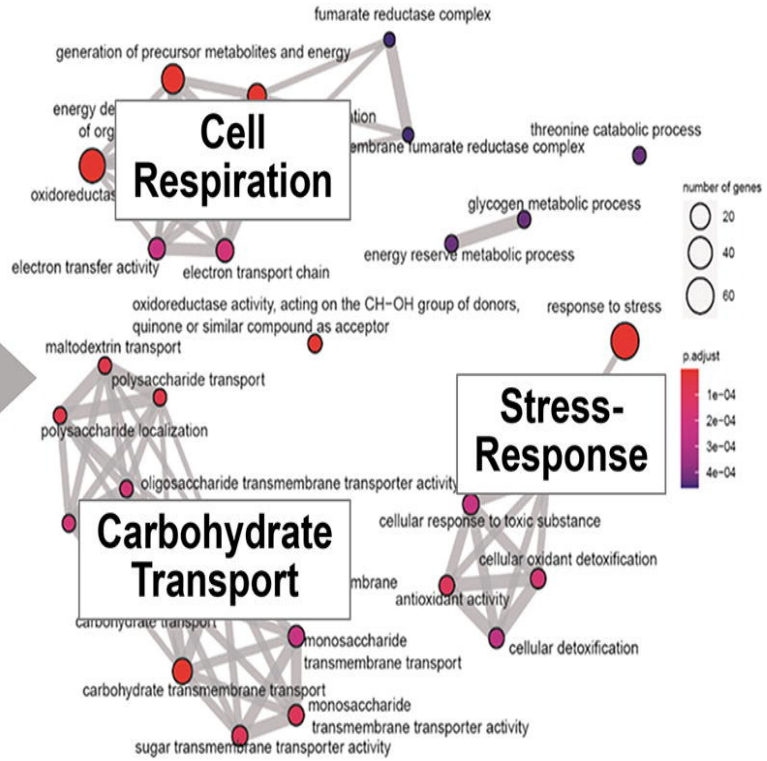
- DZ tip II, HTA
- Litiaza renala bilaterala
- Multiple episode de itu, ultimele 2 cu Klebsiella XDR pentru care Zavi+ Aztreonam sinergism
- Motivele internarii:

	Enterobacterales					
	Class A Carbapenemase (*e.g.* KPC)	**Class B Carbapenemase (*e.g.* NDM)**	**Class D Carbapenemase (*e.g.* OXA-48)**	***Pseudomonas aeruginosa***	***Acinetobacter baumannii***	***Stenotrophomonas maltophilia***
Ceftobiprole						
Ceftolozane-tazobactam						
Ceftazidime-avibactam						
Cefiderecol						
Meropenem-vaborbactam						
Imipenem-relebactam						
Aztreonam-avibactam						
Plazomicin						
Eravacycline						



Carbapenemase producing *K. pneumoniae* harboring hypervirulence plasmids

Antibiotic tolerant population of *K. pneumoniae*



RNA-Seq Pathway Analysis

- Hypervirulent K. pneumoniae (hvKP) infections are associated with metastatic infections among healthy hosts in the community.
- These infections have mortality rates of up to ~40% and significant morbidity, including visual and neurological impairment. Virulence in hvKP is primarily attributed to siderophore production and increased capsule polysaccharide (CPS).
- Although infections caused by hvKP are associated with high rates of morbidity and mortality, these strains have historically retained high rates of susceptibility to antibiotics.

Dosing of antibiotics for carbapenem-resistant Enterobacterales infections in adults with normal renal function

Class	Agent	Dosage
Standard-spectrum antibiotics other than carbapenems, if susceptible		
Fluoroquinolones	Ciprofloxacin	400 mg IV every 8 hours or 750 mg orally every 12 hours
	Levofloxacin	750 mg IV or orally once daily
Sulfonamides	Trimethoprim-sulfamethoxazole (co-trimoxazole)	Simple cystitis: 1 double-strength tablet (trimethoprim 160 mg and sulfamethoxazole 800 mg) orally every 12 hours. Infections other than simple cystitis: 8 to 12 mg/kg/day (trimethoprim component) IV or orally in 2 or 3 divided doses (eg, 2 double-strength tablets orally every 12 hours for a patient who weighs 70 kg). Maximum: 960 mg (trimethoprim component) per day.
Aminoglycosides	Gentamicin*	Simple cystitis: 5 mg/kg IV for one dose Infections other than simple cystitis: 7 mg/kg IV for the first dose with subsequent doses and dosing intervals based on pharmacokinetic evaluation
	Tobramycin*	Simple cystitis: 5 mg/kg IV for one dose Infections other than simple cystitis: 7 mg/kg IV for first dose with subsequent doses and dosing intervals based on pharmacokinetic evaluation
	Plazomicin*	Simple cystitis: 15 mg/kg IV for one dose Infections other than simple cystitis: 15 mg/kg IV for first dose with subsequent dosing interval adjusted if needed based on trough concentration
Other standard-spectrum antibiotics	Nitrofurantoin¶	Simple cystitis: Macrocrystal/monohydrate (Macrobid) 100 mg orally every 12 hours
	Fosfomycin¶	Simple cystitis: 3 g orally for one dose
	Minocycline△	200 mg IV or orally every 12 hours
Carbapenem antibiotics, if susceptible		
Carbapenems	Meropenem	Simple cystitis: 1 g IV every 8 hours (infuse each dose over 30 minutes) Infections other than simple cystitis: 2 g IV every 8 hours (infuse each dose over 3 hours)◇
	Imipenem-cilastatin	Simple cystitis: 500 mg IV every 6 hours (infuse each dose over 30 minutes) Infections other than simple cystitis: 500 mg IV every 6 hours (infuse each dose over 3 hours)◇
Novel extended-spectrum antibiotics		
Advanced beta-lactamase inhibitor combinations§	Ceftazidime-avibactam	2.5 g IV every 8 hours (infuse each dose over 2 to 3 hours)◇
	Meropenem-vaborbactam	4 g IV every 8 hours (infuse each dose over 3 hours)◇
	Imipenem-cilastatin-relebactam	1.25 g IV every 6 hours (infuse each dose over 30 minutes)
Siderophore cephalosporin	Cefiderocol	2 g IV every 8 hours (infuse each dose over 3 hours)◇
Novel tetracycline derivatives	Tigecycline△	200 mg IV loading dose, followed by 100 mg IV every 12 hours
	Eravacycline△	1 mg/kg/dose IV every 12 hours
Combination therapy¥	Ceftazidime-avibactam **plus** Aztreonam	Ceftazidime-avibactam 2.5 g IV every 8 hours (infuse each dose over 3 hours)◇ **plus** Aztreonam 2 g IV every 8 hours (infuse each dose over 3 hours) administered at the same time as ceftazidime-avibactam, if possible

This table lists typical doses for use in CRE infection among patients with normal renal function. Antimicrobial susceptibility should be confirmed for clinical isolates. Higher doses may be warranted for infections of the central nervous system.

CRE: carbapenem-resistant Enterobacterales; IV: intravenously; OXA-48: OXA-48-like carbapenemases.

* Aminoglycosides can be used as monotherapy for susceptible CRE urinary tract infections (UTIs) when other options are limited. They should not be used as single agents for infections outside the urinary tract. For patients >120% of ideal body weight, use adjusted body weight for aminoglycoside dosing; a calculator is available. For selection of dosing weight and determination of dose adjustments, refer to UpToDate content on dosing and administration of aminoglycosides.

¶ Nitrofurantoin and fosfomycin are effective for simple cystitis but neither agent should be used for complicated UTIs (eg, pyelonephritis) or for infections outside the urinary tract. Fosfomycin should only be used for simple cystitis caused by *E. coli*.

△ Tigecycline and eravacycline are effective for intra-abdominal infections, but data supporting their use for CRE infections at other anatomical sites are scarce. Minocycline should not be used a monotherapy for intra-abdominal infections. None of these agents should be used to treat UTIs or bacteremia because they may not achieve adequate levels in the urine or blood.

◇ May administer first dose first dose over 30 minutes when rapid attainment of therapeutic drug concentrations is desired.

§ These agents have no activity against metallo-beta-lactamase carbapenemase (MBL)-producing isolates. Additionally, meropenem-vaborbactam and imipenem-cilistatin-relebactam have limited intrinsic activity against OXA-48-like-producing isolates.

¥ We generally avoid combination therapy. An exception is the combination of ceftazidime-avibactam and aztreonam for MBL-producing isolates.

Reference:

1. *Tamma PD, Aitken SL, Bonomo RA, et al. IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections: Version 1.0. Infectious Diseases Society of America. Available at: https://www.idsociety.org/practice-guideline/amr-guidance (Accessed October 4, 2022).*

CONCLUZII

1. **Rezistenta antimicrobiana nu are granite fiind un fenomen intalnit peste tot in lume. Amploarea acestui fenomen variaza insa in functie de coordonatele geografice. Pe harta Europei, zona de S-E, unde este amplasata si Romania, cuprinde tari cu o incidenta crescuta a rezistentei antimicrobiene.**

2. **Principalele cauze care au contribuit la escaladarea fenomenului de rezistenta antimicrobiana sunt: consumul crescut de antibiotice, lipsa diagnosticului etiologic, nerespectarea regulilor de prevenire a raspandirii intraspitalicesti a germenilor MDR.**

3. **Diagnostic stewardship – implica un algoritm in ce priveste utilizarea performanta a mijloacelor de laborator pentru a avea identificare cat mai rapida a agentului etiologic, pentru ca in situatiile amenintatoare de viata suntem „contra cronometru”.**

4. Imbunatatirea diagnosticului stewardship prin introducerea tehnicilor de biologie moleculara de identificare rapida bacteriana si a mecanismelor de rezistenta face parte din efortul comun de a scadea consumul de antibiotice la nivel de spital, cu implicatii asupra rezistentei antimicrobiene.

5. Balanta cost-eficienta trebuie judecata prin prisma conservarii eficientei antibioticelor existente printr-o mai buna utilizare a lor.

- 6. Infectiile cu germeni cu rezistenta crescuta la antibiotice necesita terapii de salvare care sunt extrem de costisitoare.
- 7. Scurtarea timpului pana la identificarea agentului etiologic poate influenta decisiv prognosticul pacientului, poate conduce la scurtarea perioadei de spitalizare si la reducerea costurilor totale.
- 8. Raspandirea la nivel intraspitalicesc a acelor tulpini considerate ,,high risk clones” poate conduce la aparitia de focare si la o rata crescuta de deces a pacientilor infectati, existand foarte putine optiuni terapeutice.