Resistance bactérienne en hématologie

Recommandations de l'ECIL

CC 5/10/2012

Pourquoi de nouvelles recommandations?

2) Evolution péjorative de la sensibilité des bactéries aux ATB / 2000-2010 dans le monde entier

- Hors US: surtout *Italie, Espagne, Turquie, Grèce, Roumanie… Israël, Maghreb, Inde*
- Mortalité importante chez l'immunodéprimé
- Applicabilité des recos US?

3) Très peu de nouveaux ATB +++

Les grands messages internationaux pour réduire la consommation d'ATB

- Optimiser le Dg des infections
- Préserver les anciens ATB *mais lesquels*?
- Trouver de nouveaux ATB à cible étroite (pb pour les ttt empiriques!)
- Développer les autres stratégies anti-infectieuses: vaccins, immunothérapie …
- Prévenir la transmission des BMR
- Le bon usage des ATB et la surveillance:

« le stewardship »

Inappropriate initial therapy predicts increased mortality

Multiple studies show that failure to cover resistant pathogens, including ESBL-producers, significantly and independently impairs outcomes for haemato-oncology patients

Elting *et al. Clin Infect Dis* 1997
Ariffin *et al. Int J Infect Dis* 1999
Tumbarello *et al. Antimicrob Agents Chemother* 2006
Ortega *et al. J Antimicrob Chemother* 2009
Trecarichi *et al. J Infect* 2009
Martinez *et al. Antimicrob Agents Chemother* 2010
Trecharichi *et al. Haematologica* 2011

Q1: Factors in choosing a regimen

- Local bacterial epidemiology and resistance patterns
- Patient's prior colonization or infection by resistant pathogens, particularly:
  - *MRSA and MRSE, especially with vancomycin MICs ≥2 mg/L*
  - *Vancomycin-resistant enterococci*
  - *ESBL- or carbapenemase- producing Enterobacteriaceae*
  - *A. baumannii, Pseudomonas* spp. *& S. maltophilia*
- Other patient-related factors
  - *Other risk factors for infection due to resistant pathogens*
  - *Clinical presentation*

The main factors to analyze in choosing empirical therapy of fever during neutropenia

Risk factors for infection with resistant bacteria	Risk factors for a complicated clinical course
Prior colonization or infection by resistant pathogens, particularly: ESBL- or carbapenemase- producing Enterobacteriaceae Non-fermenters*: A. baumannii, Pseudomonas* spp. & *S. maltophilia* MRSA, VRE Previous exposure to broad-spectrum antibiotics **Serious illness** (e.g. end-stage disease, sepsis, pneumonia) **Prolonged or repeated hospital stay** Urinary catheters **Older age** ICU stay	Shock, hemodynamic instability, hypotension Localized infection (e.g. pneumonia, enteritis, catheter infection) **Inpatient status** Prolonged and severe aplasia **Co-morbidities** (bleeding, dehydration, organ failure, chronic illness) **Advanced age (> 60y)** Inadequate initial antibiotic therapy

Définition d'une stratégie d'escalade

"Escalation therapy"

- Initial empirical therapy covers typical Enterobacteriaceae and *P. aeruginosa*, but not ESBL or carbapenemase producers, nor multi-resistant non-fermenters
  - *(e.g. ceftazidime, cefepime or piperacillin-tazobactam)*
- If the patient deteriorates, or a resistant pathogen is isolated, therapy is 'escalated', *e.g. from cefepime to a carbapenem*

Définition d'une stratégie de désescalade
De-escalation therapy

– Initial empirical regimen is very broad, with coverage of multi-resistant Gram +ve and –ve pathogens (e.g ESBL-producers)

  • *e.g. carbapenem + anti-MRSA agent*

– Therapy is de-escalated to a simpler or narrower spectrum ('targeted') therapy once the microbiology lab does not report resistant pathogens

Stratégie d'escalade

- **Pour:** Evite l'usage intempestif et exagéré des ATB, dont les carbapénemes
  - *Moindre toxicité, moindre coût*
  - *Moindre sélection de résistance aux pénèmes*
- **Contre:** Le pronostic individuel, pénalisé par l'insuffisance possible des 48 premières heures de traitement

Tumbarello *et al. Antimicrob Agents Chemother* 2006
Trecarichi *et al. J Infect* 2009
Ortega *et al. J Antimicrob Chemother* 2009
Martinez *et al. Antimicrob Agents Chemother* 2010

Stratégie de désescalade

- **Pour:** Probablement plus efficace sur les 48 premières heures, jusqu'aux résultats microbios (*bénéfice individuel attendu*)
- **Contre:** Usage empirique possiblement abusif des ATB à plus large spectre chez un grand nombre de pts=> risque accru de sélection de R (surtout pénèmes). *Compromet le "bénéfice collectif"*

General strategy for the empirical treatment of febrile neutropenia-I

Initial regimen targeted on the most prevalent bacteria at the centre, unless the patient

- *is seriously ill at presentation or*
- *is known to be colonized with resistant bacteria or*
- *has had an infection with resistant bacteria*

If these risk factors apply, initial treatment may be modified

ECIL Guidelines for Empirical Treatment of Febrile Neutropenia

Escalation Strategy

Escalation should be employed for patients with

- *An uncomplicated presentation*
- *Without specific risk factors for resistant pathogens*
- *In centres were infections due to resistant pathogens are rarely seen at the onset of febrile neutropenia* ***BII***

ECIL Guidelines for Empirical Treatment of Febrile Neutropenia

De-escalation Strategy

De-escalation should be applied for patients

- *With complicated presentations*
- *With individual risk factors for resistant pathogens,*
- *In centres where resistant pathogens are regularly seen at the onset of febrile neutropenia* ***BII***

Suggested initial regimens in an escalation strategy

- **Use <u>non</u>-carbapenem β-lactam**
  - *<u>No</u> coverage* vs. *resistant Gram +ve bacteria such as MRSA & vancomycin-resistant enterococci*
  - *<u>No</u> combination with aminoglycoside / quinolone*

Suggested initial regimens in a de-escalation strategy

- Carbapenem monotherapy
- Anti-pseudomonal β-lactam + aminoglycoside or quinolone
  - *With carbapenem as the β-lactam in seriously ill-patients*
- Colistin + β-lactam or rifampicin *etc*.
- Early coverage of resistant-Gram +ves with a glycopeptide or newer agent

Initial empirical therapy for febrile, high-risk patients with uncomplicated neutropenia

- Anti-pseudomonal ceph (cefepime*, ceftazidime*) **AI**
- Piperacillin-tazobactam **AI**
- Other possible options include:
  - Anti-pseudomonal carbapenem** **AI**
  - Ticarcillin-clavulanate, cefoperazone-sulbactam

* Avoid if ESBLs are prevalent

** AI for efficacy, but should be avoided in uncomplicated patients lacking risk factors for resistant bacteria, to preserve activity for seriously-ill patients

First-line carbapenems should be reserved for situations where:

- Known colonization or previous infection with:
  - *ESBL-producing Enterobacteriaceae*
  - *Gram -ves resistant to narrower-spectrum β-lactams* **BII**
- Seriously-ill patients
  - *e.g. presentation with septic shock, pneumonia* **BII**
- Centres with a high prevalence of infections due to ESBL-producers at the onset of febrile neutropenia
  - *Should also prompt infection control review* **BIII**

Initial therapy in patients colonised or previously infected by resistant Enterobacteriaceae

Resistance type	Treatment
ESBL	*Carbapenem** ***BII***
Carbapenemase	*Colistin** ***CIII*** + β-Lactam +/- <u>one</u> of : *Tigecycline** ***CIII*** *or* *Aminoglycoside* ***CIII*** *or Fosfomycin* ***CIII***

*Freifeld *et al. Clin Infect Dis* 2011

Initial therapy in patients colonised or previously infected by resistant non-fermenters BIII

Bacteria	Treatment
β-lactam resistant *P. aeruginosa*	Colistin + *β-lactam* +\- fosfomycin
β-lactam resistant *Acinetobacter*	Colistin + *β-lactam* +/- tigecycline
S. maltophilia	Co-trimoxazole + *β-lactam* (preferable ticarcillin-clavulanate) +\- moxifloxacin

Hachem *et al*. *Antimicrob Agents Chemother* 2007
Falagas *et al. J Antimicrob Chemother* 2008
Peleg *et al. Clin Microbiol Rev* 2008

Options ATB des infections à CG+ vanco-R

Oxazolidinone (linezolid) **AII**

- *May delay marrow recovery*

Cyclic lipopeptide (daptomycin) **BII**

- *Not if pneumonia present*

Streptogramin (quinupristin/dalfopristin) **BIII**

Glycylcycline (tigecycline) **BIII**

- *Low blood levels*
- *Limited experience with VRE*
- *FDA Drug Safety Communication: Increased risk of death with tigecycline compared to other antibiotics used to treat similar infections, especially ventilator-associated pneumonia*
- *Few data with febrile neutropenia*

Options ATB pour les entérobactéries carbapenem-R

The following antibiotics should be combined with other antibiotics active *in vitro*, unless they are the only active agents

- Colistin +… **BII**
  - *A loading dose and high maintenance dose may be required*
- Tigecycline +… **BIII**
  - *Low blood levels; ineffective in ventilator-associated pneumonia; FDA Drug Safety Communication: Increased risk of death with tigecycline compared to other antibiotics used to treat similar infections, especially ventilator-associated pneumonia*
- Aminoglycosides + … **BIII**
- Fosfomycin +… **CIII**

- For colistin, tigecycline, aminoglycoside and fosfomycin resistant pathogens consult ID / microbiologist **CIII**

Options ATB pour les *P. Aeruginosa bétalactam-R*

- Colistin +…* **AII**
- Fosfomycin +…* **CIII**
- For *P. aeruginosa* resistant to colistin, β-lactams, quinolone, aminoglycoside and fosfomycin – consult ID/microbiologist **CIII**

* Use combined with other agents active *in vitro*; if these are the only active antibiotics - consult ID/microbiologist

Options ATB pour les *Acinetobacter spp.* Betalactam R

- Colistin +…* **BIII**
- Tigecycline +…* **BIII**
  - Low blood levels
  - Not effective in ventilator-associated pneumonia
  - FDA Drug Safety Communication: Increased risk of death with tigecycline compared to other antibiotics used to treat similar infections, especially ventilator-associated pneumonia
    - Use combined with other agents active *in vitro*, if they are the only active antibiotics - consult ID/microbiologist