1st European Conference on Infection in Leukemia

Empirical antibacterial treatment - Aminoglycosides

Sept. 30th / Oct. 1st 2005 Juan-les-Pins - France

ELN European LeukemiaNet

EBMT

EORTC European Organisation for Research and Treatment of Cancer

ICHS International Conference on Hospital Acquired Infections in Immunocompromised Hosts

Background

Goals of initial empirical antibacterial combination therapy:

- Broad spectrum coverage
- Bactericidal concentrations
- Synergistic effect
- Prevention of bacterial resistance

Where is the place of beta-lactam + aminoglycoside combination in the treatment of febrile neutropenic patients (especially high-risk population) ?

Questions I

1) Should AG be given as upfront empirical therapy in febrile neutropenic patients ?

   (if not: Are there some specific indications for AG upfront empirical therapy?)

2) Should AG be given in patients with persistent fever after initiation of broad spectrum empirical ATB ? (modification)

Questions II.

3) Should AG be given in case of microbiologically-documented infection in febrile neutropenic patients ? (all patients? in specific conditions ?)

4) What is the optimal administration schedule for AG in neutropenic patients ? (once-daily or multiple daily regimens ?)

Aminoglycosides in guidelines

- **NCCN** (v. 1.2004)

1.line : in combination with antipseudomonadal beta-lactam if:

- high risk of *P. aeruginosa* infection (prior infection, ecthyma gangrenosum, invasive disease) or clinically unstable patient (hypotension)

Aminoglycosides in guidelines

- **NCCN** (v. 1.2004)

Modification:

- consider to add AG if the patient (with high risk od Pseudomonas infection) has persistent fever on monotherapy or is unstable or Pseudomonas infection is microbiologically documented

OD dosing: not recommended as a standard treatment

Aminoglycosides in guidelines

- **IDSA** (Hughes et al., 2002)

1. line: beta-lactam + AG may be used for management of complicated cases and/or if resistance is a problem

Monotherapy = combination (A-1)

Aminoglycosides in guidelines

- **IDSA**

Modification: AG may be added in case of progressive infection, documented resistant Gram-negative infection

OD dosing: not recommended as a standard treatment

Aminoglycosides in guidelines

- **AGIHO/DGHO** (Link et al., 2003)

1. line: AG + beta-lactam may be used

Modification: may add AG in case of persistent fever, if initial monotherapy failed, according to clinical conditions and sensitivity of pathogen

OD dosing: optional (preferrably use NET and AMI)

Study flow chart

Potentially relevant articles: 256

Not relevant: 549

Total articles retrieved: 805

Excluded: pharmacokinetic, microbiological “in vitro” or epidemiological studies: 103

Excluded: trials in which an antibiotics combination (e.g glycopeptides, quinolones, cotrimoxazole) was evaluated with or without an aminoglycoside: 38

Excluded: other reasons: 32

75 randomised controlled trials
comparing beta-lactam monotherapy vs. beta-lactam-aminoglycoside combination therapy for high-risk febrile neutropenia included (66 assessed as part of existing meta-analyses)

9 randomised controlled trials comparing once daily vs. thrice-daily aminoglycoside treatment for febrile neutropenia included (4 assessed as part of existing meta-analyses)

Scope of the review: Final evaluation

- 2 meta-analyses
  (Furno et al., 2002; Paul et al., 2003)
- 9 trials/articles
- 15 abstracts from proposed meetings

Betalactam monotherapy versus betalactam-aminoglycoside combination therapy in cancer patients with neutropenia

Paul M, Soares-Weiser K, Grozinsky S, Leibovici L

The Cochrane Database of Systematic Reviews 2003, Issue 3

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46 RCT; 7642 patients; 583 bacteremic episodes; 58 with Ps. aeruginosa

Results

- Primary outcome measure: all cause mortality

  No significant difference between monotherapy and combination (also in six subgroups): RR 0.85

- Secondary outcome measure: treatment failure

  no difference in 9 trials comparing the same betalactam RR 1.12

  advantage to monotherapy in 37 trials comparing different betalactams (mainly for patients with documented infection or with hemat. malignancy) RR 0.86

  advantage to combination treatment in patients with severe neutropenia RR 1.49

Results

- **Superinfections**

  bacterial: no difference

  fungal: more frequent in combination group (not significantly different)

- **Adverse events**

  significantly more frequent in combination group RR 0.42 for nephrotoxicity (risk higher also in trials using OD regimens- RR 0.20)

  discontinuation of study drugs more often in combination group

Monotherapy or aminoglycoside-containing combinations for empirical treatment of febrile neutropenic patients: a meta-analysis

Furno P, Bucaneve G, Del Favero A

The Lancet Infectious Diseases, Vol 2, April 2002

29 RCT, 4795 febrile episodes, subset of 1029 bacteremic episodes

Results

- Outcome measure: treatment failure
- Odds ratios for individual studies favor monotherapy in 20 studies, combo in 8 studies
- Pooled odds ratio of clinical failure with monotherapy versus combo = 0.88
- Subgroup analyses (pts with severe neutropenia; „higher quality“ studies) : no significant difference
- Subgroup analyses (pts > 14 years; bacteremic episodes) : marginally significant differenc in favour of monotherapy)

Monotherapy is as effective as combination of betalactam plus aminoglycoside

Literature not analysed in meta-analyses

- 9 trials were identified

  The results of our analysis have not found different results compared with both meta-analyses

Question 1

- Is betalactam monotherapy as efficacious as betalactam plus AG combination as initial empirical therapy in AL or HSCT febrile neutropenic patients ?

YES (AI)

overall response (resolution of fever or infection without initial regimen modification)

response in documented Gram-neg. infections

overall survival

infection-related mortality

Question 2
Is betalactam plus aminoglycoside combination more toxic than betalactam monotherapy ?

YES

Nephrotoxicity (AI)

Ototoxicity (AI)

Questions 3/4

- Are there data supporting the empirical addition of AG to the inital antibiotic regimen in patients with persistent fever?

NO (CIII)

- Are there data supporting the addition of AG to the inital antibiotic regimen in case of microbiologically-documented gram-negative infection ?

NO (CIII)

Question 5

- Is once-daily dosing of AG as efficacious as and less toxic than multiple dosing regimen in febrile neutropenic patients ?

YES (AI)
Supported by data in non neutropenic patients

Questions 6-10

- **Is there any evidence supporting the use of beta-lactam + AG combination in neutropenic patients:**

1. **With high suspicion (i.e.: local epidemiology) of resistant gram-negative infections, including *Ps. aeruginosa*: YES (C III)**
2. **For severe sepsis and septic shock: YES (C III)**
3. **For pneumonia: NO (C III)**
4. **For preventing the emergence of resistance during empirical treatment: NO (B I)**

Problem	Recommendation	Grading
BL monotherapy is as efficacious as BL+AG as empirical therapy of febrile neutropenia	YES	A I
BL+ AG combination is more nephrotoxic and ototoxic than BL monotherapy	YES	A I
OD dosing of AG are as efficacious as and less nephrotoxic than MDD	YES	A I
Empirical addition of AG to the initial regimen in patients with persistent fever	NO	C III
Empirical use of BL+AG combination in patients in whom a resistant Gram-negative infection[2] is suspected	YES	C III
Addition of AG to the initial regimen in case of documented *P. aeruginosa* infection	NO	C III
Use of BL+AG combination in patients with severe sepsis or septic shock	YES	C III
Use of BL+AG in neutropenic patients with pneumonia	NO	C III
Use of BL+AG combination to prevent emergence of resistance during therapy	NO	B I

Suggestions

Choice of appropriate beta-lactam for monotherapy according to

- local epidemiology and resistance data
- recent beta-lactam use
- available evidence

Discontinuation of AG when resistance is ruled out or no Gram-negatives have been isolated

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