**Title**

Old antibitiotics, new solutions: old narrow spectrum betalactamine and cotrimoxazole with PK/PD optimization as a treatment for gram negative bacteria in ICU.

**Authors**

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Introduction :

The use of broad-spectrum antibiotics, including an anti-anaerobic spectrum, is associated with the emergence of multi-resistant bacteria. However, all the new molecules on the market targeting GNB are very broad-spectrum, implying a strong ecological impact. Particularly in resuscitation, the volume of antibiotic prescriptions is very high. It is necessary to limit the pressure of antibiotic selection by using molecules with a narrower spectrum and less ecological impact. We propose to use in the existing pharmacopoeia the narrow spectrum molecules whose optmisation of PK/PD parameters would allow them to be used as an alternative to Carbapenems, third and fourth generation Cephalosporins or fluroquinolones.

Methods :

Systematic review of the literature allowing in a first step to select antibiotics active against GNB with a low ecological impact. In a second step, a literature review will allow to define the modalities of use of the selected molecules for the optimization of the PK/PD parameters integrating dosage, stability data and infusion modalities.

Results and Discussion :

Cefoxitin, temocillin, Amoxicillin ac clavulanic, aztreonam, piperacillin, piperacillin tazobactam, cotrimoxazole were selected for their lower ecological impact and their possible integration in an antibiotic stewardship program in intensive care.

We propose continuous infusion administration methods to optimize the PK/PD parameters of its time-dependent molecules at maximum doses.

With the objective of optimizing the dosage of antibiotics at the place and time of infection in ICU, we take into account the special profil of the patients in ICU as hypoalbuminemia.

In case of Acute Kidney Injury, we do a first day at full doses, and the latter at the dosage adapted to the GFR.

When an Augmented Renal Clearance was diagnosed, we increased the doses, and made some dosages.

Under the conditions of use in intensive care, the stability data allow the use of electric syringes for the infusion of temocillin, aztreonam and cefoxitin, the other molecules will have to be used with a volumetric pump.Each continuous infusion begins with a bolus.

1/ COTRIMOXAZOLE

It has a bacteriostatic effect on cocci gram plus in monotherapy, and a bactericidal effect in biotherapy.

Inoculum effect have been reported, with it time dependent activity.

It can be diluted in G5% or in Nacl 0.9% : at the ratio of 1/20 . It stability is 4h at 25°C.

We use maximum doses in adults of Sulfamethoxazole 1200 mg + trimethoprim 240mg x4/ day by intra veinous administration in 4 hours by Volumetric pump.

2/CEFOXITIN

It has a bactericidal effect.

No clear inoculum effect have been reported, with it time dependent activity.

It can be diluted in Nacl 0.9% : at the ratio of 1g on 10ml. It stability is 24h at 25°C.

We use maximum doses in adults of 12g/ day by intra veinous administration in 24 hours by Volumetric pump.

3/TEMOCILLIN

It has a bactericidal effect.

Inoculum effect have been reported, with it time dependent activity.
It can be diluted in Nacl 0.9% : at the ratio of 80mg/ml . It stability is 24h at 25°C.
We use maximum doses in adults of 8g/day by intra veinous administration in 24 hours by Volumetric pump.

4/AZTREONAM
It has a bactericidal effect.
Inoculum effect have been reported, with it time dependent activity.
It can be diluted in Nacl 0.9% : at the ratio of 100mg/ml . It stability is 24h at 25°C.
We use maximum doses in adults of 12g/day by intra veinous administration in 24 hours by Volumetric pump.

5/PIPERACILLINE + TAZOBACTAM
It has a bactericidal effect.
Inoculum effect have been reported, with it time dependent activity.
It can be diluted in Nacl 0.9% : at the ratio of 4g/50ml . It stability is 24h at 25°C.
We use maximum doses in adults of 24g/day by intra veinous administration in 24 hours by Volumetric pump.

6/AMINOSID
It has a bactericidal effect.
Post antibiotic effect have been reported, with it concentration dependent activity.
It can be diluted in Nacl 0.9% or G5% : at the ratio of 20mg/ml . It stability is 24h at 25°C.
We use maximum doses in adults of 30mg/kg/day by intra veinous administration in 30 minutes by Syringe pump.

7/ AMOCICILLIN + CLAVULANIQ ACID
It has a bactericidal effect.
Inoculum effect have been reported, with it time dependent activity.
It can be diluted in Nacl 0.9% : at the ratio of 20mg/2ml . It stability is 4h at 25°C.
We use maximum doses in adults of 8g/day, by intra veinous administration of 2g per 4 hours by Volumetric pump.

Figure 1 : Uses of antibiotics in ICU

| Molecule | **Maximum concentration after dilution** | **Dilution solution** | **Stability duration according to temperature**[a] | **Prescribed daily dose** | **Minimum dilution volume** | **Dilution and administration volumétric pump** | **Dilution and administration Electic syringe** |
|---|---|---|---|---|---|---|---|
| **Amoxicillin acid clavulanic** | 20/2 mg/ml | NaCl 0.9% | 4h at 25°C | 3g | 150ml | 1g in 50ml in 4h x3/j | 1g in 50ml in 4h x3/j |
| | | | | 6g | 300ml | 2g in 100ml in 4h00 x3/j | NC |
| | | | | 8g | 450m | 2g in 100ml sur 4h00 x4/j | NC |
| **Aztreonam** | 100 mg/mL | NaCl 0.9% | 24 h at 37 °C | 6 g | 60 mL | 6 g in a 96 mL–4 mL/h pump, 24 h | |
| | | | | 8 g | 80 mL | 8 g in a 96 mL–40 mL/h pump, 24 h | |
| | | | | 10 g | 100 mL | 10 g in a 120 mL–5 mL/h pump, 24 h | |
| | | | | 12 g | 120 mL | 12 g in a 120 mL–5 mL/h pump, 24 h | |
| **Cefoxitin** | 100 mg/mL | NaCl 0.9% or G5% | 24 h at 37 °C | 6 g | 60 mL | 6 g in a 65–2.7 mL/h pump, 24 h | |
| | | | | 8 g | 80 mL | 8 g in a 96–4 mL/h pump, 24 h | |
| **Piperacillin + tazobactam** | 80 mg/mL + 10 mg/mL | NaCl 0.9% | 24 h at 25 °C | 12 g | 150 mL | 12 g in a 150 mL–6.2 mL/h pump, 24 h | |
| | | | | 16 g | 200 mL | 16 g in a 240 mL–10 mL/h pump, 24 h | |
| **Piperacillin** | 80 mg/mL | NaCl 0.9% | 24 h at 25 °C | 12 g + 1,5 g | 150 mL | 12 g/1,5 g in a150 mL–6.2 mL/h pump, 24 h | |
| | | | | 16 g + 2 g | 200 mL | 16 g/2 g in a 240 mL–10 mL/h pump, 24 h | |
| **Temocillin** | 80 mg/mL | NaCl 0.9% | 24 h at 25 °C (SPC data) | 4 g | 50 mL | 4 g in a 50 mL–2 mL/h pump, 24 h | |
| | | | | 6 g | 75 mL | 6 g in a 96 mL–4 mL/h pump, 24 h | |

Conclusions :

An antibiotic stewardship policy in resuscitation can integrate alternatives to molecules with high ecological impact with the use of Cefoxitin, temocillin, piperacillin, aztreonam and cotrimoxazole in continuous infusion using electric syringes or volumetric pumps.