Optimizing the use of antibiotics: from resistance to PK-PD-based approaches

UCL Bruxelles - Thursday April 7th 2005

As a clinician, what do I do with the available information and what is best for my patient?

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2 examples of management of antibiotic treatment:

- dose-dependent antibiotic: ciprofloxacin

- time-dependent antibiotic in continuous infusion: ceftazidime

What bacteriological information is routinely available?

- **Antibiogram**
  - rapid information on susceptibility to numerous antibiotics at the same time
  - approximate value: suitable only for S / I / R classification

- **MIC (E-test®)**
  - more precise information on susceptibility to a given antibiotic (valid to within one dilution)

What PK/PD information is routinely available?

- **Antibiotic concentration**
  - trough level: reliable concentration
  - peak level: exact times of injection of antibiotics and of blood sampling essential but often missing in practice
  - continuous level: seen with continuous injection - reliable concentration
- **Peak serum level of antibiotic / MIC**
  - dose-dependent antibiotics: key parameter = peak/MIC
- **Δ T**
  - time-dependent antibiotics: key parameter = Δ T (we evaluate Δ T using trough concentrations and occasionally samples taken between 2 injections)

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Management of FQ treatment:

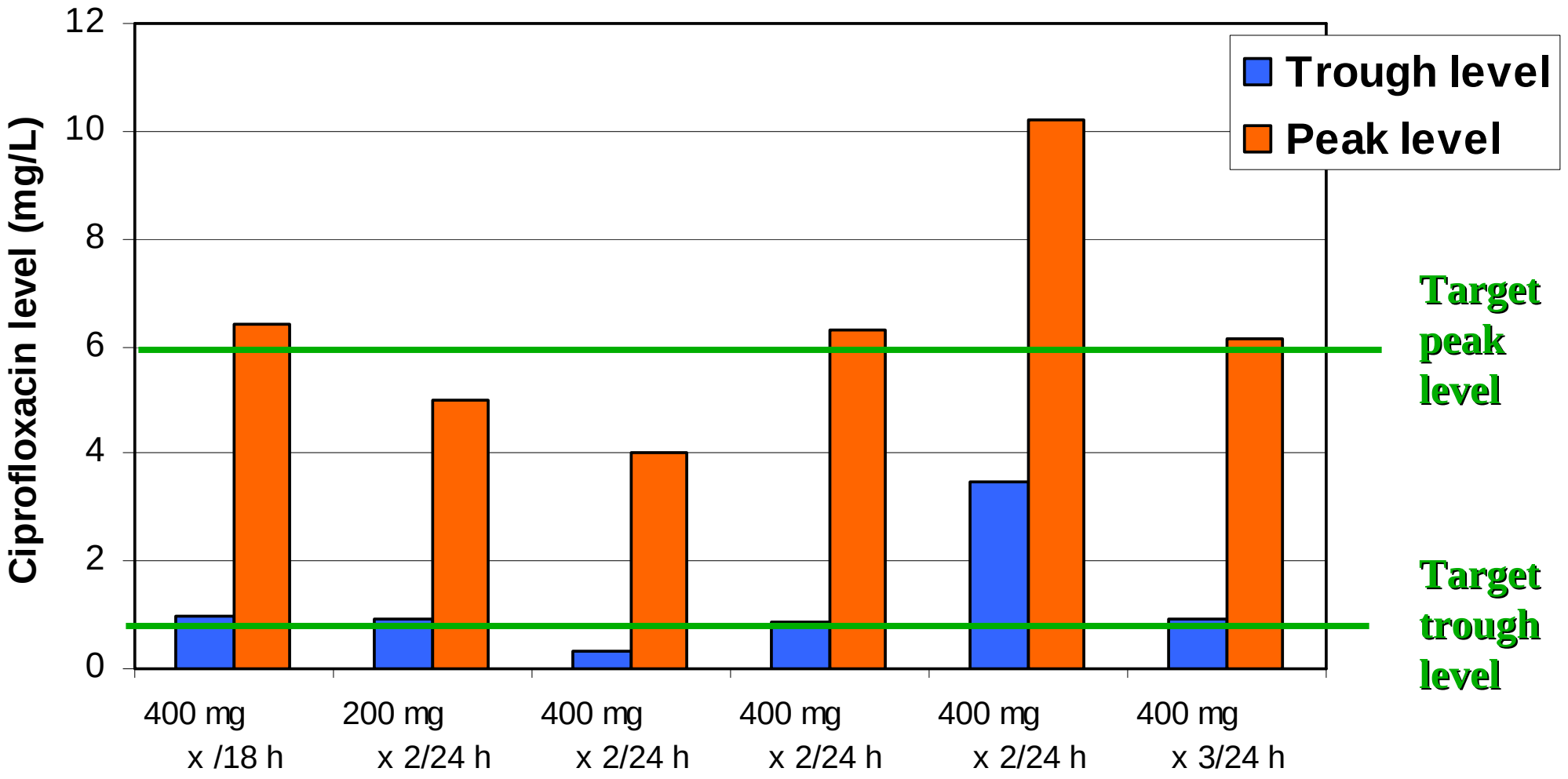
Patient: C. Maurice, 67 years old, ICU,
***E. coli* chest infection**
MIC of ciprofloxacin = 0.5 mg/L by E-Test®
Treatment: ciprofloxacin + cefotaxime (1 g x 4/24 h)

HPLC assay of ciprofloxacin in serum (mg/L)

Date	Dosage (24 h)	*Trough level	**Peak level	Peak/MIC
D2 04/08/04	400 mg x 3	5.73	10.52	21
D4 06/08	200 mg x 3	0.55	2.44	5
D6 08/08	400 mg x 2	0.19	7.23	14.5
D8 10/08	400 mg x 2	0.82	8.19	16

*before next infusion **3mn following infusion

Serum ciprofloxacin levels for 6 patients



11 strains of *E. coli* (2 reference strains and 9 clinical strains)

Strain	Phenotype	Mutation *gyrA/parC*	Antibiogram API bioMérieux
1	Nal S/Oflo S	0 / 0	S
2	Nal S/Oflo S	0 / 0	S
3	Nal R/Oflo S	+ / 0	S
4	Nal R/Oflo S	+ / 0	S
5	Nal R/Oflo S	+ / 0	S
6	Nal R/Oflo I	+ / 0	S
7	Nal R/Oflo R	+ / 0	S
8	Nal R/Oflo R	+ / 0	S
9	Nal R/Oflo R	+ / +	S
10	Nal R/Oflo R	+ / +	S
11	Nal R/Oflo R	+ / +	S

Activity of ciprofloxacin on 11 strains of *E. coli*

Strain No.	Phenotype	Mutation *gyrA/parC*	Antibiogram API bioMérieux	MIC E-test method	MPC (mg/L)
1	Nal S/Oflo S	0 / 0	S	0.012	0.12
2	Nal S/Oflo S	0 / 0	S	0.023	0.25
3	Nal R/Oflo S	+ / 0	S	0.094	0.25
4	Nal R/Oflo S	+ / 0	S	0.125	0.5
5	Nal R/Oflo S	+ / 0	S	0.25	1
6	Nal R/Oflo I	+ / 0	S	0.5	4
7	Nal R/Oflo R	+ / 0	S	0.5	2
8	Nal R/Oflo R	+ / 0	S	0.5	6
9	Nal R/Oflo R	+ / +	S	1.5	4
10	Nal R/Oflo R	+ / +	S	1.5	3
11	Nal R/Oflo R	+ / +	S	1.5	4

Strain susceptible if MIC ≤ 1 mg/L

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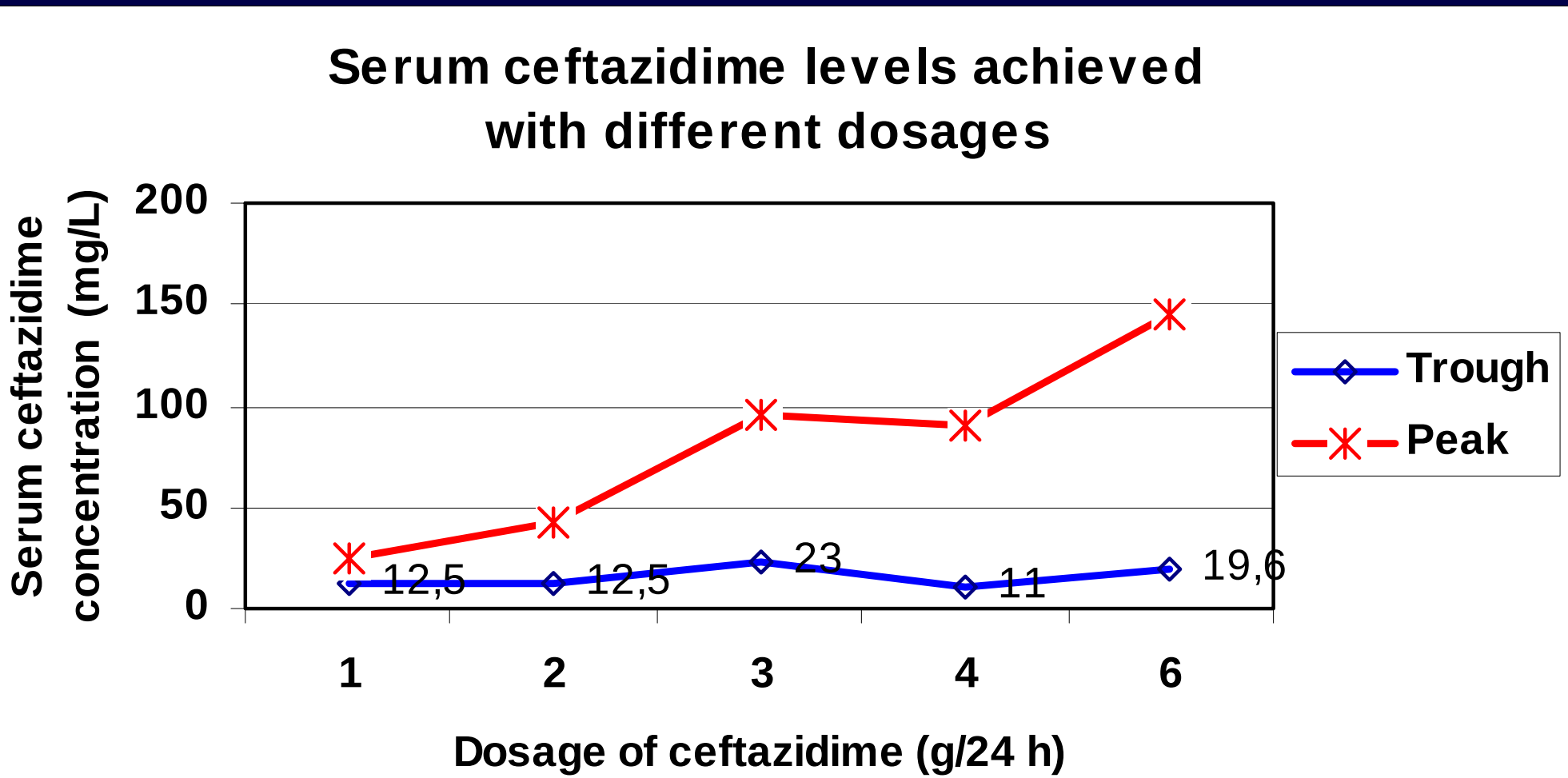
Serum ceftazidime levels achieved with different dosages
Serum ceftazidime concentration (mg/L)
200
150
100
50
0
12,5
12,5
23
11
19,6
1
2
3
4
6
Dosage of ceftazidime (g/24 h)
Trough
Peak

Value of IQ following dosage adjustment of ceftazidime (continuous infusion) for *P. aeruginosa* infection

MIC (mg/L) of ceftazidime	Conc./MIC for C = 11 mg/L Dosage: 4 g/24 h	Conc./MIC for C = 19.6 mg/L Dosage: 6 g/24 h
0.5	22	39
1	11	19.6
2	5.5	9.8
4	2.8	4.9

Conc.: serum ceftazidime concentration

CONCLUSION

The case for PK/PD-guided treatment management

Why?

When?

How?

What we still need?

CONCLUSION

Why? For serious infections and bacterial strains of limited antibiotic susceptibility:
- confirm the efficacy of the antibiotic,
- avoid toxicity of treatment,
- aim to achieve efficacy as early as possible to avoid selection of resistant mutants, particularly in strains having limited susceptibility to antibiotics.

When? Especially at the start of treatment for certain types of patient (critical care, immunocompromised, change in weight/renal function).

How? MIC, serum level, IQ.

What we still need? AUC_{24h}/MIC, time-killing curve of sera (dynamique method…).