Optimising ciprofloxacin dosing in intensive care patients based on pharmacodynamic target attainment

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Background & Objective

- The fluoroquinolone ciprofloxacin is widely used to treat nosocomial infections in intensive care patients as well as other severe infections caused by Gram⁻ pathogens. However, its use is associated with an increased development of bacterial resistance.
- Our objective was to explore, using PK/PD indices and Monte Carlo simulations, different dosage regimens of ciprofloxacin for the empirical treatment of intensive care patients with respect to both clinical efficacy and bacterial resistance.
  - The AUC_{24h}/MIC ratio was used as a predictor of clinical efficacy (Fig. 1)
  - The time within the mutant selection window (T_{MSW}) was used as a predictor of the development of bacterial resistance (Fig. 2)

Fig. 1: The AUC/MIC ratio

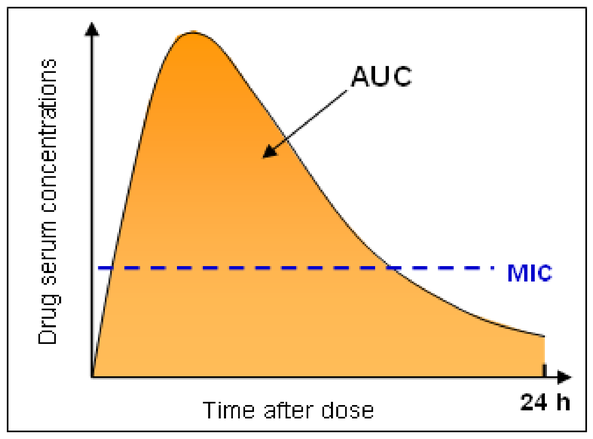
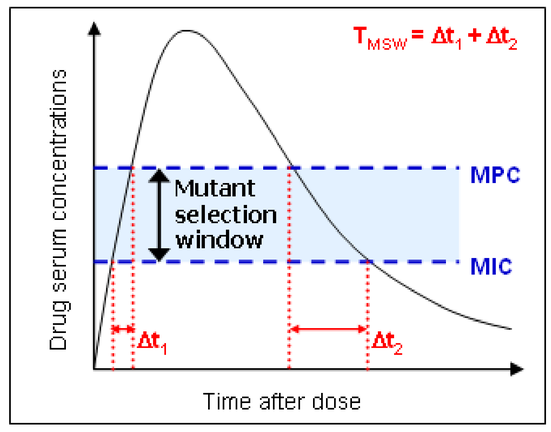


Fig. 2: Time within the mutant selection window (T_{MSW})

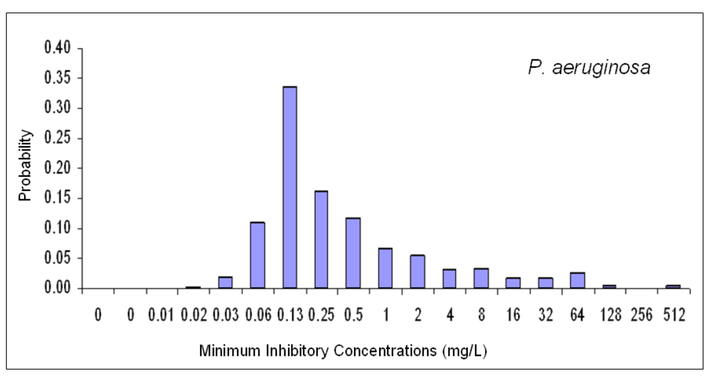


MIC: minimum inhibitory concentration, MPC: mutant prevention concentration

Material and Methods

- Two simulations trials were conducted. Trial 1 took into account the whole MIC distribution for each causative pathogen in line with empirical antibiotherapy. The distributions of MIC were taken from the website of EUCAST (European Committee on Antimicrobial Susceptibility Testing). The MIC distribution of *P. aeruginosa* is shown as an example in Fig. 3. Trial 2 used the MIC breakpoints established by the French antibiogram committee in order to treat the "worst-case" scenario. Mutant prevention concentrations (MPC) were simulated assuming a uniform distribution of MPC/MIC ratio over [4;16] [3-5].
- Free ciprofloxacin serum concentrations were simulated for 10^4 patients for a number of ciprofloxacin dosage regimens within the limit of 2400 mg/day (using Crystal Ball software). A previous population PK model was used for simulation: this model was developed in 102 ICU patients from the University Hospital of Toulouse-Rangueil, France, and included creatinine clearance as a covariate [1]. Creatinine clearance was assumed to follow a uniform distribution over [30;120] mL/min and the unbound fraction of ciprofloxacin a uniform distribution over [0.6;0.8] [2].
- Targets to achieve were: free AUC_{24h}/MIC ≥ 90h (equivalent to total AUC_{24h}/MIC ≥ 125h) [6] and T_{MSW} ≤ 20% [7].

Fig. 3: Example of MIC distribution taken from EUCAST (European Committee on Antimicrobial Susceptibility Testing)



Results

- The percentages of patients who were adequately exposed to ciprofloxacin (i.e. who reached the targets as defined above for the main Gram⁻ pathogens) are displayed in Table 1.
- For the common dosage regimens of 400 mg q12h and 400 mg q8h, low percentages of patients showed adequate exposure for *P. aeruginosa* and *A. baumannii* with respect to T_{MSW} (32-46%), while suboptimal percentages were observed for AUC_{24h}/MIC (52-70%). Increasing the daily dose did not allow major improvements (the best target attainment rates we might expect for these two pathogens were 66-79% for AUC_{24h}/MIC ≥ 90h and 58-61% for T_{MSW} ≤ 20%).
- Trial 2 showed that ≤18% of patients reached the target of T_{MSW} ≤20% for MIC breakpoints of 0.5 and 1 mg/L, regardless of the administered dose (see Fig. 4).

Table 1: Probability of attaining targeted PK/PD indices (free AUC_{24h}/MIC and T_{MSW}) with ciprofloxacin as empirical antibiotherapy against several Gram-negative pathogens in intensive care patients

Ciprofloxacin Daily dose (mg)	Rate of attainment of $fAUC_{24}$/MIC target (%) ≥90 h						
	ESC	EA	EC	KP	PM	AB	PSA
400	90	52	85	78	82	33	45
600	91	54	88	82	84	43	57
800	92	56	89	84	86	52	63
1200	93	58	91	86	87	59	70
1600	93	59	92	87	88	63	74
1800	93	60	93	88	88	64	75
2400	93	62	94	89	89	66	79

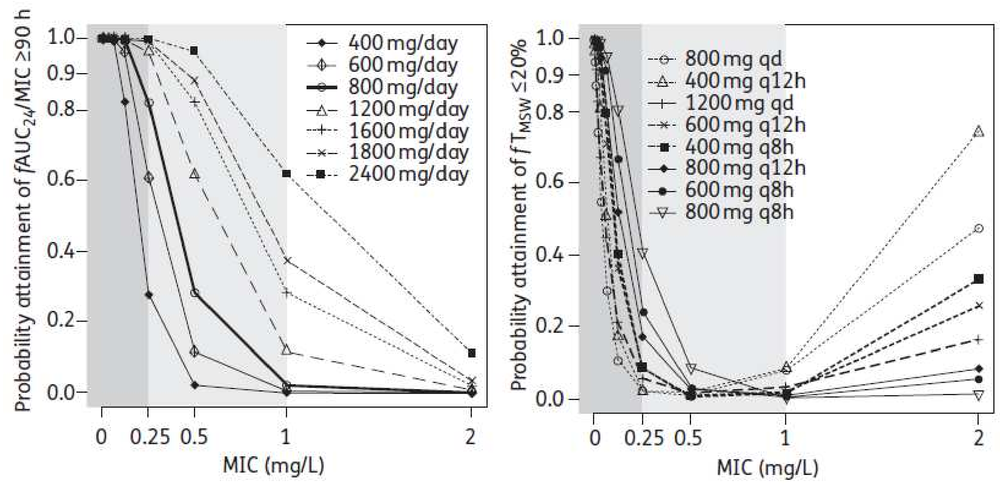
Ciprofloxacin Dosage regimen	Rate of attainment of fT_{MSW} target (%) ≤20%						
	ESC	EA	EC	KP	PM	AB	PSA
200 mg twice daily	76	62	70	48	52	39	29
200 mg thrice daily	88	70	79	62	68	39	30
800 mg once daily	72	59	68	49	51	37	25
400 mg twice daily	88	71	80	66	70	41	32
1200 mg once daily	79	63	73	58	59	39	28
600 mg twice daily	92	75	84	74	76	46	38
400 mg thrice daily	94	78	86	76	80	46	41
800 mg twice daily	94	77	86	78	80	51	45
600 mg thrice daily	95	81	90	82	83	54	51
800 mg thrice daily	96	82	90	85	84	61	58

ESC, *Escherichia coli*; EA, *Enterobacter aerogenes*; EC, *Enterobacter cloacae*; KP, *Klebsiella pneumoniae*; PM, *Proteus mirabilis*; AB, *Acinetobacter baumannii*; PSA, *Pseudomonas aeruginosa*. MIC distributions were obtained from the EUCAST website (http://www.eucast.org).

Conclusion

Based on the mutant selection window concept, our simulations question the use of ciprofloxacin for the treatment of *A. baumannii* and *P. aeruginosa* infections in ICU patients due to the potential for developing resistance. They also suggest that the breakpoints of antibiograms should be used with caution and should probably be revised.

Fig. 4: Probability of target attainment of $fAUC_{24h}$/MIC ≥90 h (left side) and fT_{MSW} ≤20% (right side) at in vitro MIC values varying from 0.002 to 2 mg/L



Dark grey: area with maximum efficacy, light grey: area with maximum likelihood of selecting resistance, white: area with minimum efficacy and a lower likelihood of selecting resistance.

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Acknowledgment: Dalia Khachman was supported by a doctoral scholarship from the Lebanese National Council for Scientific Research.