Comment on: Effectiveness and safety of an institutional aminoglycoside-based regimen as empirical treatment of patients with pyelonephritis (letter to the editor)

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Sir,

We wish to compliment Elbaz *et al*.[1] for investigating the effectiveness and safety of aminoglycoside-based regimens in the empirical treatment of pyelonephritis. Aminoglycosides have favourable pharmacokinetics allowing once-daily dosing with high urinary concentrations and demonstrate good *in vitro* activity against Enterobacterales and *Pseudomonas aeruginosa*. Therefore, especially in the era of increasing resistance, aminoglycosides might be (re)considered as interesting alternatives or add-ons.

We applaud the authors for their work.[1] Although retrospectively studied, they showed that patients treated with aminoglycosides had a significantly lower 30 day mortality rate compared with those treated with β-lactams or fluoroquinolones. Also, in subgroup analyses, aminoglycoside-based treatment consistently performed better than (or at least similar to) the comparator, while not leading to a higher incidence of nephrotoxicity.[1]

Since the authors mentioned that their guidelines are based on 'pharmacokinetic (PK)/pharmacodynamic (PD) principles', we wanted to evaluate the dosing regimens used. Because aminoglycosides act in a concentration-dependent manner, we were surprised to find a rather conservative dosing regimen in their supplementary data,[1] especially for amikacin (i.e. 15 mg/kg in patients with a CL_{CR} >80 mL/min), which was recommended for hospital-acquired infections. We have shown that higher amikacin dosing (at least 25 mg/kg) is mandatory to attain the PK/PD target, a C_{max}/MIC ratio of at least 8, correlating with clinical efficacy.[2] When

taking into account the EUCAST breakpoints for Enterobacterales and *P. aeruginosa* (8 mg/L), 60% of patients did not attain this target with 15 mg/kg.[2,3] The need for higher doses has been endorsed by several others.[4,5] As resistance proportions in Israel were found to be similar to those in southern Europe, higher dosing regimens are advised to reach the PK/PD target in order to tackle more resistant microorganisms.[6] Next to higher dosing, regular peak level monitoring is recommended when aminoglycosides are used for several days to follow up attainment of the PK/PD target, and if not, doses should be increased.[7] It seems that only trough level monitoring was recommended in order to warrant safety.[1]

Finally, the protocol recommended dose adjustments based on CL_{CR}, with reductions of up to 4 mg/kg for amikacin and 2.5 mg/kg for gentamicin in patients with a CL_{CR} between 30 and 40 mL/min.[1] In order to maximize efficacy, this should be discouraged especially for the loading dose, which is installed independent of renal function. For maintenance doses, extending the dosing interval instead of lowering the dose will reduce trough levels (and the risk for renal toxicity) without affecting the peak concentration.

As shown by Elbaz *et al.*,[1] there was a trend to a more favourable outcome of non-aminoglycoside regimens versus amikacin in patients treated for hospital-acquired infections. In their cohort, it might be interesting to report peak concentrations and evaluate whether these exceeded the actual MIC (or the EUCAST breakpoint) by at least 8-fold. This could subsequently be used to test associations between C_{max}/MIC attainment and 30 day mortality, which would provide pivotal clinical evidence (that is currently lacking) for the three key pillars reflecting PK/PD-based aminoglycoside dosing: use of high initial doses, peak concentration monitoring and dosing interval extension, rather than dose reduction.

Transparency declarations

All authors declare that they have no competing interests.

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