

## Ceftolozane-tazobactam versus levofloxacin in urinary tract infection

Florian Wagenlehner and colleagues (May 16, p 1949)<sup>1</sup> report an industry-sponsored randomised controlled trial comparing ceftolozane-tazobactam with levofloxacin in complicated and upper urinary-tract infection. The trial results should be questioned because the design was biased against the control drug and breached the guiding principles of antibiotic stewardship.<sup>2</sup>

The choice of empirical antibiotics should be guided by local resistance profiles,<sup>3</sup> but in this trial,<sup>1</sup> patients from 202 international sites were given identical regimens. In the control group, 27% of isolates were resistant to levofloxacin, making it an inappropriate empirical choice, and figure 3 in the Article<sup>1</sup> confirms that the superiority of ceftolozane-tazobactam was driven by the subgroup with isolates resistant to levofloxacin.

A guiding principle of antibiotic stewardship is de-escalation to the narrowest spectrum antibiotic possible once culture results are available.<sup>2</sup> De-escalation was not permitted in either group and it is likely that many patients received inappropriately broad-spectrum drugs, putting them at unnecessary risk of complications.

Another guiding principle is early intravenous-to-oral switching, which reduces costs, risk of line infection, and length of hospital stay.<sup>4</sup> No intravenous-to-oral switching was allowed in the trial and some patients were therefore exposed to unnecessary risk of line infection.

Although ceftolozane-tazobactam might have a place in empirical treatment in settings where resistance rates to narrower spectrum drugs are high, it is vital that antibiotics are compared on a level playing field and study protocols adhere to basic standards of care, which includes the guiding principles of antibiotic stewardship.

I declare no competing interests.

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- 1 Wagenlehner FM, Umeh O, Steenberg J, Yuan G, Darouiche RO. Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI). *Lancet* 2015; **385**: 1949–56.
- 2 Leekha S, Terrell CL, Edson RS. General principles of antimicrobial therapy. *Mayo Clin Proc* 2011; **86**: 156–67.
- 3 Koningstein M, van der Bij AK, de Kraker ME, et al. Recommendations for the empirical treatment of complicated urinary tract infections using surveillance data on antimicrobial resistance in the Netherlands. *PLoS One* 2014; **9**: e86634.
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Florian Wagenlehner and colleagues<sup>1</sup> compared ceftolozane-tazobactam with levofloxacin for the treatment of complicated urinary-tract infections. We are concerned about the fact that the intravenous dose of levofloxacin for the 7-day study period was tailored to a measured baseline creatinine clearance, which is very time-consuming and might be hampered by errors in the urine collection. If indeed an estimation of the creatinine clearance using the Cockcroft-Gault formula was done, this seems to be the least appropriate calculation. A 2011 Kidney Disease: Improving Global Outcomes statement recommends that “Glomerular filtration rate should be the standard measure to evaluate kidney function for staging of chronic kidney disease and drug dosing purposes”.<sup>2</sup> Because levofloxacin is mainly (>85%) eliminated via the kidneys, it was necessary to adjust dosing in 128 of the 402 patients treated with levofloxacin that had mild and moderate renal impairment. Dose reduction rather than extension of the dosing interval might have had a detrimental effect on the action of levofloxacin, which offers the best clinical and microbiological outcome at a peak concentration to minimum inhibitory concentration ratio of at least 12:2.<sup>3</sup> In our view, at least the loading dose should have

been 750 mg levofloxacin in all patients randomised to that group to achieve adequate peak concentrations. Because data suggest a relation between the use of oral fluoroquinolones and acute kidney injury, possibly aggravated by the concomitant use of angiotensin-converting-enzyme inhibitors and angiotensin-receptor antagonists,<sup>4</sup> assessment of renal function at the end of the 7-day study period would have been of interest in the study cohort with a high proportion of hypertensive patients.

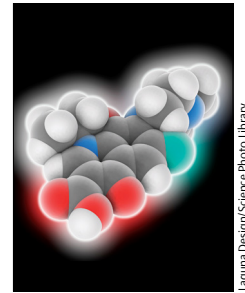
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- 1 Wagenlehner FM, Umeh O, Steenberg J, Yuan G, Darouiche RO. Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI). *Lancet* 2015; **385**: 1949–56.
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The ASPECT-cUTI trial by Florian Wagenlehner and colleagues<sup>1</sup> reported that intravenous ceftolozane-tazobactam was not only non-inferior but also superior to intravenous levofloxacin in the composite of microbiological eradication and clinical cure of complicated urinary tract infections. In view of the increasing rate of bacteria resistant to fluoroquinolones, these findings are not unexpected.<sup>2,3</sup> In the Netherlands, recent recommendations by the ISIS-AR study group<sup>4</sup> no longer endorse the use of fluoroquinolones as first-line empirical treatment of complicated urinary-tract infections, but suggest initial combination treatment with either amoxicillin or amoxicillin-clavulanic



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acid, or a second or third generation cephalosporin and an aminoglycoside. Furthermore, the rate and class of concomitant active non-study antibiotics needs to be reported for both treatment groups because an imbalance between these might affect overall study results. Interestingly, the differences in composite cure rates were considerably different between the two individual trials that had been pooled into the ASPECT-cUTI trial (2.5%, 95% CI –6.3 to 11.2 vs 14.5%, 5.8 to 22.9) in the microbiological modified intention-to-treat population. Because the second individual trial largely drives the superior effect of the pooled trial with regard to the composite cure rate, it would be of interest for the clinician to be informed of the differences in patient characteristics between both individual trials.

We declare no competing interests.

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- 1 Wagenlehner FM, Umeh O, Steenbergen J, Yuan G, Darouiche RO. Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI). *Lancet* 2015; **385**: 1949–56.
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### Authors' reply

We thank Tom Boyles, Jan Kielstein and Julius Schmidt, and Ciprian Popa and colleagues, for their comments in response to our Article.<sup>1</sup> Our trial used a study design that tested intravenous-only therapy, which had both regulatory

and clinical precedence. We agree with Boyles that antibiotic stewardship is an important issue and that specific collateral effects can be assessed in such studies, as has been shown in two randomised trials assessing bowel colonisation with resistant Gram-negative bacilli after antimicrobial therapy of intra-abdominal infections with ertapenem versus ceftriaxone-metronidazole.<sup>2</sup> These trials showed significantly more faecal organisms producing extended-spectrum  $\beta$ -lactamase in the ceftriaxone-metronidazole group. We therefore agree that these aspects should be represented more often in clinical trials.

The comment that the superiority of ceftolozane-tazobactam was driven by the subgroup with isolates resistant to levofloxacin is true; however, ceftolozane-tazobactam was also non-inferior in levofloxacin-susceptible patients (ie, the presence of levofloxacin resistance was not the driver for achieving non-inferiority, which was the regulatory objective of this study). The absence of oral step-down therapy in the study design was attributed to the fact that the study drug, ceftolozane-tazobactam, had no oral formulation, making it difficult to find a common oral comparator that was not the test drug. Additionally, 80% of treated patients had pyelonephritis, a severe urinary-tract infection warranting intravenous therapy in most patients. In this study of more than 1000 patients, line infections were not an issue; therefore, patients were not exposed to unnecessary risks.

Popa and colleagues refer to the recent recommendations from the Netherlands<sup>3</sup> that no longer advise the use of fluoroquinolones as first-line empirical treatment of complicated urinary-tract infections. These recommendations are, however, based on nationwide surveillance data assessing only the antimicrobial coverage of different drugs for the treatment of complicated urinary-tract infection, without clear evidence of clinical success or failure of these antibiotic drug-drug

combinations. Our interventional study provides clinical evidence that levofloxacin, even when administered at the highest approved dose, might no longer be a suitable first-line empirical treatment for complicated urinary-tract infection in all geographic regions.

In reply to the comment from Kielstein and Schmidt, there are results on file that break down efficacy by degree of renal impairment. A substantial proportion of patients had normal renal function at baseline and did not need any levofloxacin dose adjustment. In this subgroup of patients, ceftolozane-tazobactam functioned creditably versus levofloxacin, attesting to the robustness of the primary outcome.

FMW has served as a consultant to Cubist Pharmaceuticals. ROD previously provided limited consulting services to Cubist Pharmaceuticals that were not related to this study and is at present involved in an investigator-initiated clinical trial of *Clostridium difficile*, funded originally by Optimer Pharmaceuticals and later Cubist Pharmaceuticals. OU is an employee of Cubist Pharmaceuticals.

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- 1 Wagenlehner FM, Umeh O, Steenbergen J, Yuan G, Darouiche RO. Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECTcUTI). *Lancet* 2015; **385**: 1949–56.
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- 3 Koningstein M, van der Bij AK, de Kraker MEA, et al. Recommendation for the empirical treatment of complicated urinary tract infections using surveillance data on antimicrobial resistance in the Netherlands. *PLoS One* 2014; **9**: e86634.

### Department of Error

Murray C, Chambers R. Keeping score: fostering accountability for children's lives. *Lancet* 2015; **386**: 3–5—The appendix for this Comment has been corrected as of Sept 25, 2015.