Author's response to reviews

Title: European S T80 Community-Associated Methicillin-Resistant Staphylococcus Aureus Orbital Cellulitis in a Neonate.

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Author's response to reviews: see over
Dear Dr Crow,

We are herewith submitting a revised version of the manuscript entitled “European ST80 Community-Associated Methicillin-Resistant Staphylococcus aureus Orbital Cellulitis in a Neonate”.

We thank very much Reviewer I for the meticulous evaluation. We address her comments:

1) We think that, as actually it was pointed out by the reviewer, there are more than one issues that could be teaching points. Having to select one, we tend to consider that a better defined teaching point can be the one on indications when treatment for Community-Associated methicillin-resistant S. aureus (CA-MRSA) should be initiated:

In a serious infection, such as orbital cellulitis, the indications that should be carefully considered as to when to initiate empirical treatment against CA-MRSA are the following: (1) clinical suspicion or imaging findings consistent with orbital abscess; (2) extreme ages, such as infants under 3 months of age, especially during the neonatal period; and (3) an area where MRSA infections are not rare (prevalence of >5%).

This teaching point has been included in the conclusions.

2) We are not aware of any study on orbital cellulitis, or on staphylococcal infections in general, showing a clinical manifestation capable to differentiate MRSA (PVL+) from MSSA (PVL+) disease.
However, we speculate that the combination of virulence and resistance tends to pose an increased risk for a difficult management and complications. It depends on the extent of drainage. As you know well, it is not always feasible to achieve extensive drainage. Sometimes, it requires difficult techniques or multiple procedures. Then, it is the antimicrobial treatment. Use of less active, possibly bacteriostatic or slow bactericidal agents, may leave the virulent PVL-positive MRSA isolate to damage valuable tissues or spread to the central nervous system or other distant foci.

The reported case was a quite severe orbital abscess. To our opinion, the appropriately selected aggressive and promptly initiated empirical therapy as well as the drainage, as much as feasible, contributed to avoiding complications and permanent sequelae.

3) We have not measured daptomycin levels. The pharmacokinetics of daptomycin in children aged 2-17 years has been well characterized (Abdel-Rahman et al. *Pediatr Infect Dis J*. 2008; Abdel-Rahman et al. *Pediatr Infect Dis J*. 2011). These studies were taken into consideration by the Infectious Diseases Society of America, in order to suggest dosages of daptomycin for the treatment of pediatric MRSA infections, such as bacteremia, septic arthritis, and osteomyelitis, in the 2010 Clinical Practice Guidelines (Liu et al. *Clin Infect Dis* 2011; 52:e18–e55). Our colleagues at the Department of Paediatrics, based on their experience during the last 5 years, consider that high dose of daptomycin is efficacious in deep seated, difficult-to-extensively-drain infections.
Regarding daptomycin levels among young infants, we have taken into consideration the available information from recent presentations or publications. Smith et al. at the Duke University have studied the pharmacokinetics of daptomycin during the first 120 days of life. They have presented data at ICAAC 2011 (abstract no. A1-1159), while the complete study is currently submitted for publication. Other published information on daptomycin levels during the first weeks of life is derived from case series or reports (Cohen-Wolkowiez et al. *J Perinatol.* 2008; Sarafidis et al. *Am J Perinatol.* 2010; Antachopoulos et al. *Infection* 2012).

4) To our knowledge, neither the presence nor the absence of clinical difference(s) among cases due to ST80 versus USA300 clone is supported by the existing literature. The number of European clinical studies on pediatric infections due to an MRSA isolate is limited. We agree with the reviewer that it is an interesting issue that needs to be evaluated in the future.

We hope that the revised version of our manuscript meets with your standards and expectations.

Yours sincerely,

Fani Zacharaki