Commentary Article

Suggested title

Time to turn off the toxins: Adjuvant suppression of group A *Streptococcus*

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Streptococcus pyogenes or Group A Streptococcus (GAS), remains a major global pathogen, responsible for a wide spectrum of disease ranging from pharyngitis to severe invasive (iGAS) infections[1]. Central to the virulence of *S. pyogenes* are its repertoire of anti-phagocytic proteins and toxins, including the superantigens. Indeed, emergence of new *S. pyogenes* lineages can be associated with both increased iGAS case frequency and mortality, often linked to changes in toxin production[2].

Given the central role of toxins, there has been long-standing interest in the use of anti-toxin approaches to improve iGAS outcomes. One strategy has been using adjunctive intravenous immunoglobulin, to neutralise circulating toxins. A second is using adjunctive clindamycin, to down-regulate bacterial production of toxins. Increased resistance to clindamycin has been reported in the USA[3], raising the question of whether it remains a viable adjunctive therapy. Like clindamycin, linezolid interferes with protein synthesis and has been used as an anti-toxin agent both in the treatment of iGAS and in severe methicillin resistant *Staphylococcus aureus* infections.

Current observational evidence supporting the use of anti-toxin therapies is mixed, and subject to significant bias, including both confounding by indication and immortal-time biases[4]. One approach to overcome immortal-time bias is the use of an emulated trial design, which controls for both the time that treatment is initiated and the probability that individuals received the intervention, to overcome limitations of traditional observational studies.

In their study, Babiker and colleagues[5] use an emulated trial approach to compare mortality between individuals with iGAS who received either adjunctive linezolid or clindamycin. Using a large, multi-centre dataset they compared outcomes in over one thousand patients, of whom about three-quarters received clindamycin and one quarter linezolid. Both groups had to have received beta lactam antibiotics for at least 3 days as well as the antitoxin agent, meaning only 3.75% of iGAS patients could be included. There were important differences in the characteristics of patients, with more cases of severe iGAS amongst individuals receiving clindamycin, and more cases of lower respiratory tract infection in those receiving linezolid.

After adjustment for covariates, there was no significant difference in outcomes related to which drug was used. Overall mortality was, however, numerically higher amongst individuals receiving linezolid in the main analysis and a number of key sub-groups including bacteraemia, severe iGAS and patients on ICU, although in each case the difference was not statistically significant. Importantly, the vast majority of deaths from iGAS are known to occur in the first 48h[6]. As the study only compared outcomes in patients who survived 3 days, the study's comparison of linezolid and clindamycin is restricted to the minority of iGAS deaths that occur 'late'. This likely explains the low iGAS mortalities compared with those reported elsewhere[6,7].

The study was undertaken in the USA where rates of clindamycin resistance are reported to be increased[3] but interestingly the presence or absence of clindamycin resistance did not impact the outcome in clindamycin-treated patients, albeit susceptibility testing was undertaken surprisingly infrequently. Importantly clindamycin resistance is much less frequent elsewhere including Canada and UK[8,9], likely linked to different circulating lineages[3].

What then is the practical message from this study? The results cannot provide guidance on iGAS adjuvant treatment in the first 3 days. However, in centres that do undertake susceptibility testing, clindamycin-resistance will be readily identified within 3 days. Hence, for those who wish to continue an antitoxin agent, this study provides some confidence that linezolid could be a viable alternative to clindamycin as an anti-toxin agent bearing in mind that, at this later time point, survival chances are anyway increased. In settings where clindamycin resistance is more frequent, use of linezolid on a 'just in case' basis could be avoided through introduction of wider susceptibility testing.

Most importantly the study is not able to answer the critical question faced by the clinician when assessing an acutely unwell patient with suspected iGAS; should I provide any form of empiric anti-toxin therapy at all? It is doubtful that any observational study, even an emulated trial design, will be able to robustly answer this question. Babiker and colleagues highlight the inherent challenges in undertaking a prospective trial to definitively answer this question. Such a trial would require a substantial sample size, require clinicians to have equipoise about providing or

withholding anti-toxin drugs to critically unwell patients, and most importantly would require randomisation and initiation of therapy empirically before definitive identification of *S. pyogenes*. These are considerable issues, but advancing our understanding of iGAS management may well require us to rise to such a challenge.

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