



## Antibiotics for Sepsis - Does Each Hour Really Count?



"Each hour's delay in initiating antibiotics costs lives" is a doctrine that has attained quasi-religious status. Like most (quasi-)religions this is founded more on faith and hope than hard fact, according to an article in press in the American Journal of Respiratory and Critical Care Medicine.

Article author Mervyn Singer, Professor of Intensive Care Medicine, Bloomsbury Institute of Intensive Care Medicine, University College London, laments the fact that the "each hour delay" mantra is being drummed into healthcare providers, hospital administrators, funders and governmental bodies. In the United Kingdom, for example, NICE is proposing a quality standard, required by healthcare commissioners, that impels antibiotics within an hour of identifying "suspected sepsis". Fearing retribution and litigation, clinicians – especially junior clinicians – may be forced to treat everyone "just in case", the author says, adding that the strength of evidence for "each hour delay" is not particularly compelling.

"To my knowledge, every theistic study supporting this dogma is based solely on retrospective analyses of databases usually collected for administrative or other reasons. Crucial items of data are usually lacking, such as confirmation of infection, and adequacy of antibiotic choice, antibiotic dosing and source control," says Prof. Singer.

Time Zero (either from when the infection starts, or organ dysfunction actually begins) and time to presentation/recognition of sepsis is largely unknown but will vary from hours to several days. "An excessive delay could be arguably injurious. However, expecting an hour-by-hour linear relationship between mortality risk and delay in antibiotic commencement from presentation/recognition lacks credibility," the author says.

He notes that Kumar et al. was the first to draw such a striking straight-line relationship in 2,154 ICU patients using delay in commencing antibiotics after the onset of hypotension. Yet they did not consider the impact of sedation related to mechanical ventilation as a confounding factor in causing hypotension, Prof. Singer points out.

The AJRCCM invited the professor to peer-review the paper by Liu et al., who mined a large administrative database from 21 Northern California hospitals and randomly selected 35,000 patients treated for presumed infection in emergency departments and subsequently hospitalised. They performed a complex adjustment for patient and hospital factors to generate a risk-adjusted odds ratio for hospital mortality of 1.09 (95% CI, 1.05-1.13) for each elapsed hour between emergency department registration and antibiotic administration.

While their headline finding sits neatly with the prevailing credo, the professor is doubtful about the

results of their adjustments. For example, compared to patients given antibiotics within the first hour, those treated at any time starting between hours 2-5 had a similar 25-30% increase in the adjusted odds risk of mortality. The risk was doubled if treatment was delayed until Hours 5-6. "So why should the first hour from ED registration be so crucial, especially when Time Zero is unknown? And why should each subsequent hour's delay until Hour 5 then not show an effect, followed by a big late rise?", writes Prof. Singer.

The author concludes, "The practice of medicine should be about appropriate risk management rather than operating within a climate of fear and penalisation. We should accept there will always be a chance of getting it wrong and try hard to minimise this risk. A more circumspect yet still time-critical approach to determine if infection is indeed present, to identify the site and likely cause of infection, to discuss optimal treatment with seniors and specialists, and to gauge any deterioration, may prove superior."

Source: [American Journal of Respiratory and Critical Care Medicine](#)

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Published on : Wed, 31 May 2017