

Antibiotics for sepsis – does each hour really count? Or is it incestuous amplification?

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Incestuous amplification - the (extreme) reinforcement of ideas and/or beliefs that occurs when like-minded people communicate with each other (1).

‘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. With the failure of other beliefs, previously touted as incontrovertible, such as the 24-hour sepsis management bundles (2) and, more recently, a specific early goal-directed therapy strategy (3), we *need* to believe we are offering some benefit to our acutely ill patients. A blind faith in the primacy of early antibiotics suits this purpose, yet I confess to being decidedly agnostic, and fearful. Increasing levels of antimicrobial resistance is rightly viewed as a global crisis (4). The indiscriminate and inappropriate use of antibiotics will only serve to accelerate this problem. Furthermore, antibiotics themselves also cause harm, for example, organ injury, mitochondrial dysfunction, the impact on the microbiome, and overgrowth by fungi and *Clostridium difficile* (5-8).

The ‘each hour delay’ mantra is however being drummed into healthcare providers, hospital administrators, funders and governmental bodies. Quality improvement programs are being driven by financial penalty. In the United Kingdom, NICE is proposing a quality standard, required by healthcare commissioners, that impels antibiotics within an hour of identifying ‘suspected sepsis’ (9). Fear of retribution and litigation will coerce the clinician – especially the junior clinician - to treat everyone ‘just in case’. A core quality measure requiring a reduction in time to first antibiotic dose for community-acquired pneumonia from 8 to 4 hours was achieved at the expense of a significant decrease in diagnostic accuracy (10).

What impact will a one-hour time limit have? Will clinician paranoia result in antibiotics being given for every hospitalized exacerbation of COPD and each child with tracheobronchitis? Will clinicians still complete a full course of antibiotics 'just in case', notwithstanding confident early exclusion of bacterial infection? (11).

The strength of evidence for 'each hour delay' is not particularly compelling. To my knowledge, every theistic study supporting this dogma are 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. Non-infectious mimics accounted for 18% of patients initially diagnosed and treated as septic in an US emergency department (ED) (12), while 13% of 2579 patients admitted to two Dutch ICUs with a presumptive diagnosis of sepsis had a *post-hoc* infection likelihood of 'none', and an additional 30% of only 'possible' (13). Inadequate early source control increased 28-day mortality from 26.7% to 42.9%, regardless of the appropriateness of empiric antibiotic therapy (14). Using *in vitro* sensitivities, empiric antibiotic regimens were ineffective in up to a third of cases with proven Gram negative bacteremia (15). These major confounders are not addressed yet surely must impact on outcomes.

Second, the raw data are heavily adjusted statistically to deliver the evangelical message. An analysis performed on 17990 patients within the Surviving Sepsis Campaign database saw no relationship between actual mortality and antibiotic commencement for up to 5 hours' delay, yet adjustment by "*[hospital] location where sepsis was suspected, geographic location [of the hospital], infection source, various organ failures, hypotension (resolved and unresolved), mechanical ventilation, and other clinical characteristics (unpublished observations)*" enabled demonstration of a 7.5% '*linear increase in the risk of mortality for each hour of delay in antibiotic administration*' (16). A further 457 patients entered into the database received no antibiotics but their outcomes were unreported.

Clearly, some adjustment is necessary. Septic patients presenting as moribund are obviously much more likely to die, yet such patients are (hopefully) more likely to be recognized and treated promptly, and not just with antibiotics. How does the speed and quality of resuscitation impact? Conversely, the grey, indeterminate case that evolves in a downhill

manner from a relatively mild initial presentation, and whose underlying sepsis belatedly declares itself, will be managed in a very different manner and may also be compromised by delays in non-antibiotic treatment. There are inherent dangers to both under- or over-adjustment of data.

Large population-based adjustments can never hope to accurately capture the intricacies and nuances of these factors. How confident can we be in the validity of the adjustments? My own faith is usually undermined by issues with biological plausibility. 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. Kumar *et al* was the first to draw such a striking straight-line relationship in 2154 ICU patients using delay in commencing antibiotics after the onset of hypotension (17). Yet they did not consider the impact of sedation related to mechanical ventilation as a confounding factor in causing hypotension. Notwithstanding the absence of “*plausible bacterial pathogen isolated or definitive radiologic, surgical, autopsy, or biopsy evidence of infection*” in 22.1% of their population, each hour of delay in initiating effective (proven or adjudicated) antimicrobial therapy was associated with a 7.6% decrease in survival. The authors excluded 558 patients in whom appropriate antibiotics were commenced pre-hypotension. Paradoxically, survival in this subset (52.2%) was *lower* than in those receiving treatment within the first five hours post-hypotension.

Kumar *et al* (17) also reported that failure to give an effective antibiotic within 36 hours was virtually a death sentence. Yet, antibiotic sensitivities are rarely reported before 36 hours and, in my experience, large numbers of these under-treated patients do survive. Indeed, nearly half of 51 reviewed studies failed to show an association between inappropriate empiric antibiotic choice and increased mortality in patients with *proven* bacteremia (18). A recent prospective study of 679 adults with Gram negative bacteremia in 10 English hospitals (15) identified initial empiric therapy as inappropriate in 34%, yet 30-day mortality was identical (15%). The authors concluded that “*outcome is determined primarily by patient and disease factors.*”

Thirdly, and perhaps most crucially, there is a striking disconnect between these and other 'positive' adjusted retrospective analyses and every prospective study I am aware of that has specifically examined the impact of antibiotic delay, some also stratifying by illness severity (14, 15, 19-23). Each of these prospective studies has *failed* to show a relationship between delay in antibiotic administration within 5-6 hours of patient presentation and mortality. They comprise sample sizes from hundreds to thousands, and populations from emergency departments, general wards and intensive care units. A 'before-after' study, ethically-approved and NIH-funded, conducted on 484 patients in the Surgical ICU of the University of Virginia, assessed outcomes in the year pre- and post-implementation of a policy of withholding antibiotics until objective microbiological confirmation of infection (23). Case mix and patient management were similar across the epochs. Remarkably, a median 10 hour overall delay in initiating antibiotics was associated with a halving in mortality rate (13% versus 27%). Even in those patients with significant hypotension, a median 16-hour delay in starting antibiotics in the conservatively-managed group was associated with a 26% mortality compared to 66% in those aggressively-managed ($p=0.0004$).

In view of this healthy (or perhaps unhealthy) scepticism, the *AJRCCM* kindly invited me to peer-review the paper by Liu *et al* (24). The authors mined a large administrative database from 21 Northern California hospitals and randomly selected 35000 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. No data were forthcoming on confirmation of infection, empiric antibiotic sensitivities, adequacy of non-antibiotic management including source control and the speed/efficacy of resuscitation.

Clearly, the authors are expert and highly respected in the field of critical care epidemiology, and I would not pretend to fully understand their sophisticated adjustments of the raw data. While their headline finding sits neatly with the prevailing credo, the results of their adjustments unfortunately also fail my biological plausibility test. 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? Of note, nearly 30% of the total cohort of patients (and 33% of total deaths) received antibiotics within Hour 0-1 but only 2.5% (and 2.5% of deaths) of the cohort had antibiotics started between Hours 5-6. Other oddities include a big increase in adjusted mortality risk for non-invasive ventilation but no difference for mechanical ventilation or heart rate, and a protective effect for altered mental status. Yet this same database was also used for the validation of the qSOFA score in which altered mental status was a major prognosticator for mortality (25).

I certainly do not advocate that antibiotics be unnecessarily delayed or withheld, especially when faced with a critically ill patient (26). Any sick patient, regardless of etiology, should be seen promptly with due consideration given to possible antibiotic prescription. However, a blanket policy of throwing antibiotics at every patient on 'suspicion' of sepsis (however vague) will carry unintended and potentially far more harmful consequences. The alternative option of a world of highly virulent, pan-drug resistant micro-organisms is far less palatable. I am yet to be convinced that each hour does matter, or in the *prima facie* argument that antibiotics make a huge difference to outcomes. Watchful waiting \pm removal of any potentially infected plastic tubing may be all that is needed in many patients. 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 minimize 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. Epidemiology studies should generate hypotheses but not dictate healthcare policy. We should not suspend belief completely but should certainly challenge it with constructive agnosticism and good science. Would the equipoise exist for prospective randomized studies of immediate versus considered antibiotic therapy?

I have no conflict of interest for my apostate, dissident views.

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