Considered judgement on quality of evidence

Key question: Does door-to-needle time have an impact on outcome?

1. Volume of evidence

Up to end of 2006

7 observational studies (4 retrospective, 3 prospective) with a total of 19592 patients from 3517 hospitals in the USA and Canada.

3 interventional studies (2 controlled before and after, 1 cluster randomised trial) with a total of 4666 patients from 68 hospitals in Scotland and the USA

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3 systematic reviews of all observational studies.

2. Applicability to the NHS in Scotland

One study performed in Scotland, all others in North America. The evidence is applicable.

3. Generalisability

The studies include Acute admissions and A & E wards in hospitals of different sizes (including teaching and small general hospitals). One study (Ziss) included children, the remaining studies all included adults only. 3 studies excluded immunocompromised patients.

4. Consistency: group judgement about conflicting evidence and overall direction of evidence

Observational studies: link with outcome

It is not possible to combine results from different studies because they do not provide data in the same format, or use different endpoints for mortality or use a different cut off for door to needle time.

With the exception of Dedier, all 5 studies with mortality data suggest that shorter door to needle time is associated with lower mortality. This trend is only statistically significant in the largest study (Houck, n= 13,771), which only included patients aged 65 or more. The study by Dedier et al used a different cut off (antibiotics within 8h of admission) and found evidence of confounding by indication (patients with more severe pneumonia were more likely to receive antibiotics within 4h of admission). This may explain why antibiotic administration within 8h of admission was associated with a non-significant increase in risk of mortality.

All 3 of the studies with length of stay data suggest that shorter door to needle time is associated with shorter length of stay. The association is statistically significant in three studies (Battleman, Houck, Ziss).

Interventional studies: impact on outcome

In both of the Controlled Before and After studies the intervention significantly improved the % of patients who received antibiotics within 4h. However, assessment of impact on outcome was confounded because there were statistically significant reductions in mortality in the control hospitals in the post-intervention hospitals in both studies. In the RCT 80% of patients in the control hospitals received antibiotics within 4h of admission. Because of this ceiling effect there were no significant differences in door to needle time between intervention and control hospitals. Consequently none of these studies provides evidence that can link changes in door to needle time with changes in outcome.

Systematic reviews: impact on outcome

Nazarian et al looked at use of target time of 4, 6 and 8 hours to first dose of antibiotic. No evidence on 6 hours.

For 4 hours, 3 best studies showed benefit (Class II evidence) on mortality but no evidence on morbidity. There were two Class III studies and one showed benefit on mortality rate and one on length of stay.

For 8 hours, Class II study showed no benefit on mortality and one class III study shows benefit on mortality.

Pines et al looked at measurement of time to first dose of antibiotic (TFAD) and its effect on outcome (mortality) and inappropriate use of antibiotics. The evidence was inconsistent. Two studies presented evidence that measuring reduced mortality and length of stay when <4h or <8h. One study had neutral conclusion – TFAD <4h had no effect on mortality or survival, and 5 studies presented evidence against measuring TFAD as it can increase use of antibiotics in non-CAP patients.

Yu et al compared use of <4h and <8 h as TFAD. The effects on outcome were inconsistent (effect of <4h target on mortality OR 0.24 – 1.99, effect of <8h target on mortality OR 0.6 – 1.69).

In conclusion, evidence fails to confirm decreased mortality with early administration of antibiotics in stable patients with CAP. Inconsistent evidence that measuring time to first antibiotic dose has benefit on outcome in CAP or has negative impact but timely administration to patients with confirmed CAP should be encouraged.

5. Clinical impact

Comment here on the potential clinical impact that the intervention in question might have – e.g. size of patient population; magnitude of effect; relative benefit over other management options; resource implications; balance of risk and benefit.

Pneumonia is one of the commonest causes of acute medical admission to hospital and has a high mortality, especially in patients with severe pneumonia. The largest study (Houck) shows a risk difference in mortality of 15%. If true this means that the NNT (number of patients who need to receive antibiotics within 4h to prevent one death) is 42. For patients who present to Accident and Emergency Units the evidence supports the IDSA guideline that antibiotics should be administered in the Unit, before transfer to the ward. For all patients the evidence suggests that shorter door to needle is associated with better outcome. The main risk from advocating a drive to reduce door to needle time for patients with pneumonia is that this may increase unnecessary antibiotic treatment of patients who do not have pneumonia (Metersky 2006). There is evidence that this happened in the USA (Wachter 2008). However, this unintended consequence was probably driven by the method of measurement based on electronic linkage of discharge diagnosis with prescribing records, which does not distinguish between patients with severe and non-severe pneumonia.

6. Other factors

Indicate here any other factors that you took into account when assessing the evidence base.

Clinical plausibility

Waterer (2006) says that "historical data on the length of time that it takes for antibiotics to make an impact on outcome makes it unlikely that a difference of a few hours in administration will impact adversely on mortality." However, in a study of 2,154 septic shock patients who received effective antimicrobial therapy only after the onset of recurrent or persistent hypotension, a strong relationship between the delay in effective antimicrobial initiation and in-hospital mortality was noted (adjusted odds ratio 1.119 [per hour delay], 95% confidence interval 1.103–1.136, $p < .0001$). In multivariate analysis (including Acute Physiology and Chronic Health Evaluation II score and therapeutic variables), time to initiation of effective antimicrobial therapy was the single strongest predictor of outcome (Kumar).

Adverse consequences

Diagnostic uncertainty is the commonest reason for delays in antibiotic treatment of patients with pneumonia. Pressurising hospitals to treat all pneumonia patients within 4h of presentation regardless of severity is likely to lead to unnecessary antibiotic treatment, especially in older patients in whom confusion may make diagnosis difficult. (Metersky, Waterer)

7. Evidence statement *Please summarise the development group's synthesis of the evidence relating to this key question, taking all the above factors into account, and indicate the evidence level which applies.*	**Evidence level**
It is biologically plausible that minimising the time to antibiotic treatment for patients with severe pneumonia will improve outcome. Evidence from the USA shows that pressurising hospital or doctors to shorten time to first antibiotic dose for all patients may increase unnecessary treatment of patients who do not have pneumonia. Consequently we do not support centrally driven financial incentives based on linkage of information from electronic patient records (Metersky, Wachter). However we do recommend that clinical teams measure door to needle time for patients with severe pneumonia and that a 4h target is supported by evidence of improved survival from severe sepsis.	2^{++}
8. Recommendation *What recommendation(s) does the guideline development group draw from this evidence? Please indicate the grade of recommendation(s) and any dissenting opinion within the group.*	**Grade of recommendation**
A 4 hour target time should continue to be included in the care bundle for patients with severe pneumonia (CURB65≥3) in line with current guidelines for prompt treatment in management of severe pneumonia (BTS) and sepsis (Surviving sepsis).	**B**