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Extended Research Article

Effectiveness of biomarker-guided duration of antibiotic treatment in children hospitalised with confirmed or suspected bacterial infection: the BATCH RCT

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Scientific summary

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Scientific summary

Background

The BATCH trial aimed to improve antimicrobial stewardship (AMS) in hospitalised children with suspected or confirmed bacterial infection, by reducing antibiotic duration with guidance from an additional procalcitonin (PCT) biomarker laboratory test. This trial aligns with the current Department of Health Five Year Strategy and is a response to research recommendations from two published National Institute for Health and Care Excellence (NICE) guidance documents (DG18 and NG15).

The trial was a pragmatic, multicentre, open-label, parallel two-arm, individually randomised controlled trial (RCT) with internal pilot phase, qualitative study and health economic evaluations. The trial assessed the use of an additional PCT test in children (aged 72 hours up to 18 years) hospitalised with suspected or confirmed infection to guide antimicrobial-prescribing decisions. In children randomised to the intervention arm, a PCT test was performed in the hospital laboratory at baseline/randomisation and every 1–3 days while on intravenous (IV) antibiotics. Children in the control arm did not have the PCT test performed.

Outcomes

The trial used a coprimary outcome of antibiotic use and safety.

- Duration of IV antibiotic use was measured in hours.
- Safety was defined as the absence of all of the following:
  - unscheduled admissions/re-admissions [to include re-admission within 7 days of discharge with infective diagnosis, unscheduled re-admission to paediatric intensive care unit (PICU) with infective diagnosis or admission to PICU with infective diagnosis].
  - retreatment for same condition within 7 days of stopping IV antibiotics (restarting IV antibiotics which have been stopped)
  - death for any reason in the 28 days following randomisation.

Secondary outcome measures

- Total duration of antibiotic use (IV and oral).
- Duration of broad-spectrum antibiotic use.
- Time to discharge from hospital.
- Suspected adverse drug reactions (ADRs) (yes or no).
- Cost of hospital episode.
- Hospital-acquired infections (HAIs) as defined by the clinical team up to day 28.
- Health utility as measured by the Child Health Utility questionnaire (CHU9D) up to day 28.
- To provide detailed understanding of parent and health professionals' attitudes to, and experiences of, participating in the BATCH RCT.

Methods

A pragmatic, multicentre, open-label, parallel two-arm, individually RCT conducted in 15 hospitals in the UK. Children aged between 72 hours and 18 years admitted to hospital and being treated with IV antibiotics for suspected or confirmed bacterial infection were randomised (1 : 1 ratio of allocation) using minimisation for age and centre and using a secure 24-hour web-based randomisation programme to a PCT-guided algorithm versus usual standard care alone.

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The sample size of 1942 was determined, based on detecting a 1-day reduction in IV antibiotic use (90% power, two-sided) and on a non-inferiority margin of 5% absolute risk difference (RD) in the composite safety outcome (90% power, one-sided), while allowing for up to 10% loss to follow-up. Semistructured qualitative interviews were also carried out with parents and healthcare professionals (HCPs).

Health economics

Health economic analysis included direct and indirect costs associated with unscheduled admissions (to ward or PICU), re-admissions, restarting IV antibiotics and HAIs. Descriptive and regression analysis was used to identify key elements of service use and cost and explored the potential impact of baseline participant characteristics on the costs and outcomes measures. Average cost per participant was estimated at the end of the treatment and the follow-up periods, respectively, and average cost per subgroup of patients was explored for the same time points. Bootstrapping and missing data imputation were performed if justified. Differences in each arm were assessed and used for the computation of an incremental cost-effectiveness ratio (ICER). A cost-effectiveness analysis assessed possible efficiency gains. An NHS perspective was used, and relevant direct medical costs were collected. Time horizon was 28 days; therefore, there was no need to consider a discount rate. Patients' health utility was measured using CHU9D up to day 28. Descriptive and regression analysis was used to identify key elements of service use and cost and to explore the potential impact of baseline participant characteristics on the costs and outcomes measures. Differences in each arm were assessed and used for the computation of an ICER. Bootstrap sampling and a complete-case analysis were conducted to access the sensitivity of our main results. A cost-effectiveness plane was constructed. Information on direct non-medical costs, such as travelling to and from the hospitals, and indirect costs, such as parents' productivity losses, was also collected.

Results

There was no evidence of a treatment effect on any primary or secondary outcome, either overall or in any subgroup. The estimated treatment effect for the composite safety outcome was consistent with non-inferiority. We therefore conclude that making the results of the PCT-guided algorithm available to clinicians was non-inferior with respect to safety and ineffective with respect to antibiotic use.

The PCT test in itself is not very expensive (£14); nevertheless, it does not contribute to a reduction in the number of hours of IV antibiotic administration. The intervention is not cost-effective as it is more expensive with no significant improvement in IV antibiotic duration, even though it resulted in a non-significant improvement in health-related quality of life (HRQoL). Productivity losses are similar in both arms. It should be noted that income losses of around £200 during a child hospital stay are significant for families.

The qualitative evaluation showed that parent perceptions on acceptability and implementation of the intervention and trial processes were largely positive, although most parents were concerned about their child having to have extra blood tests if they were in the intervention arm. HCPs took a while to become familiar with the intervention algorithm, and as the intervention test did not align with the clinical pathway, often there were delays in getting the PCT results, which meant that adherence to the algorithm was low.

In children with comorbidities, HCPs were significantly more likely to take the PCT test into consideration, with increasing number of comorbidities, although for certain comorbidities HCPs were less likely to adhere to the algorithm. On interview, HCPs stated that antibiotic duration would likely be longer in children with comorbidities, but on quantitative analysis, there was no significant difference in antibiotic duration across comorbidity subgroups.

Conclusions

We demonstrated that there was no evidence of a treatment effect on any primary or secondary outcome, either overall or in any subgroup. The estimated treatment effect for the composite safety outcome was consistent with non-inferiority. We therefore conclude that making the results of the PCT-guided algorithm available to clinicians was non-inferior with

respect to safety and did not result in reduced antibiotic duration in hospitalised children with suspected or confirmed bacterial infection. Parental and HCP acceptability of the intervention was generally positive, although adherence was low, due to the intervention not being integrated into the routine care pathway.

Clinicians may be reluctant to adhere to biomarker-guided algorithms, due to unfamiliarity with interpreting the test result. In the presence of robust AMS programmes to reduce antibiotic use, a PCT-guided algorithm may offer little added value. Future trials must include an implementation framework to improve trial intervention fidelity, and repeated cycles of education and training to facilitate implementation of biomarker-guided algorithms into routine clinical care.

Trial registration

This trial is registered as ISRCTN11369832.

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