Procalcitonin-guided duration of antibiotic treatment in children hospitalised with confirmed or suspected bacterial infection in the UK (BATCH): a pragmatic, multicentre, open-label, two-arm, individually randomised, controlled trial

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Summary

Background Procalcitonin is a rapid response biomarker specific for bacterial infection, which is not routinely used in the UK National Health Service. We aimed to assess whether using a procalcitonin-guided algorithm would safely reduce the duration of antibiotic therapy compared with usual care, in which C-reactive protein is the commonly used biomarker.

Methods The BATCH trial was a pragmatic, multicentre, open-label, parallel, two-arm, individually randomised, controlled trial conducted in 15 hospitals in England and Wales. Children aged 72 h to 18 years who were admitted to hospital and were being treated with intravenous antibiotics for suspected or confirmed bacterial infection and who were expected to remain on intravenous antibiotics for more than 48 h were enrolled. Participants were randomly assigned (1:1) to receive either current clinical management alone (usual care group) or clinical management with the addition of a procalcitonin test guided algorithm (procalcitonin group). Participants were randomly assigned by minimisation, with site and age group (0–6 months, 6 months to 2 years, 2–5 years, and older than 5 years) as minimisation factors and a random element to reduce predictability. Participants were randomly assigned remotely using a secure 24 h web-based randomisation programme. The coprimary outcomes were duration of intravenous antibiotic use, assessed for superiority, and a composite safety measure, assessed for non-inferiority (non-inferiority margin 5%). The primary analysis sample for each coprimary endpoint included all randomly assigned participants with available outcome data. This trial is registered with the International Standard Randomised Controlled Trial Number registry, ISRCTN11369832.

Findings Between June 11, 2018, and Oct 12, 2022, 15 282 children were screened for eligibility, 1949 of whom were randomly assigned to receive procalcitonin-guided antibiotic therapy (n=977) or usual care (n=972). The median intravenous antibiotic duration was 96·0 h (IQR 59·5–155·5) in the procalcitonin group and 99·7 h (61·2–153·8) in the usual care group (hazard ratio 0·96 [95% CI 0·87–1·05]). 78 (9%) of 917 participants in the procalcitonin group and 85 (9%) of 904 participants in the usual care group had at least one event covered by the composite safety outcome measure (estimated adjusted risk difference –0·81% [95% CI upper bound 1·11]).

Interpretation In children with suspected or confirmed bacterial infection admitted to hospitals in England and Wales for intravenous antibiotic treatment of at least 48 h, the introduction of a procalcitonin-guided algorithm did not reduce duration of intravenous antibiotics treatment and is non-inferior to usual care for safety outcomes. Therefore, evidence does not support the use of procalcitonin-guided algorithms where robust effective paediatric antibiotic stewardship programmes are established.

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Introduction

Increasing antimicrobial resistance (AMR) is responsible for a substantial burden of infection with antibiotic-resistant bacteria globally.[1] The burden of AMR, measured in number of cases, attributable deaths, and disability-adjusted life-years, affects all age groups, and is highest in infants (younger than 1 year), followed by those aged 65 years or older.[2] High rates of antibiotic consumption in high-income and upper-middle-income countries in North America, Europe, and the Middle East have been reported.[3] Unnecessary and excessive use of antibiotics contributes to increasing AMR; therefore, reducing antibiotic treatment duration is a key component of hospital antimicrobial stewardship interventions.[4]

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See Online for appendix

Research in context

Evidence before this study

A formal literature search was not conducted as the research question was a recommendation from the National Institute for Health and Care Excellence 2015 evaluation of procalcitonin testing to guide antibiotic therapy for the treatment of sepsis, which included the systematic review. A systematic review and cost-effectiveness analysis conducted by the National Institute for Health and Care Excellence in 2015 evaluated procalcitonin testing to guide antibiotic therapy for the treatment of sepsis. Further studies were recommended to adequately assess the effectiveness of adding procalcitonin algorithms to guide antibiotic treatment in hospitalised adults and children with suspected or confirmed serious bacterial infection. A more recent systematic review and meta-analysis of hospitalised adult patients reported that procalcitonin-guided antibiotic therapy was effective and safe in the reduction of antibiotic duration in patients with sepsis and respiratory tract infections. There was no difference in length of hospitalisation, recurrence of infection or rehospitalisation, or 28-day mortality, but in-hospital mortality was significantly reduced.

Added value of this study

To our knowledge, this is the first large, multicentre, randomised controlled trial of a procalcitonin-guided algorithm to guide intravenous antibiotic duration in children admitted to hospitals in England and Wales with suspected or confirmed bacterial infection. Compared with usual care to guide decisions about antibiotic discontinuation and de-escalation, the use of a procalcitonin-guided algorithm did not reduce the duration of intravenous antibiotic use and was non-inferior in terms of safety. A cost-effectiveness analysis concluded that procalcitonin-guided antibiotics management was more costly than usual care without a significant reduction in intravenous antibiotic duration.

Implications of all the available evidence

Procalcitonin-guided algorithms to guide antibiotic discontinuation in children are unlikely to be effective in reducing the duration of intravenous antibiotic treatment, especially in hospitals where robust antimicrobial stewardship programmes are already implemented. Implementation of procalcitonin tests to guide antibiotics treatment decisions requires training and embedding with scenario testing, as clinicians' unfamiliarity with a procalcitonin test algorithm interpretation might make it difficult to trust the result and adhere to the algorithm's recommendation. Procalcitonin-guided algorithms should be tested in subgroups of paediatric patients to establish whether they are effective in reducing the duration of intravenous antibiotic treatment among patients with specific clinical characteristics.

Most antibiotic treatment in children with suspected bacterial infection is prescribed empirically due to the non-specific presentation of infection, urgency of treatment in the emergency department especially for infants and young children, and the lack of accurate, rapid tests to reduce diagnostic uncertainty.[5] Blood tests currently used in the UK National Health Service (NHS), such as C-reactive protein, do not reliably differentiate between serious bacterial infection, viral infection, and inflammation, and show a delayed response (12–24 h) to bacterial infection. Procalcitonin is a more specific host-response biomarker for bacterial infection, released in response to inflammatory stimuli, with very high levels produced in serious bacterial infections.[6] In contrast to C-reactive protein, procalcitonin is a reliable biomarker that changes early in the course of bacterial infection and correlates with clinical progression, enabling real-time monitoring and facilitating clinical decisions for monitoring progression of serious bacterial infection and response to antimicrobial therapy, and for informing initiation, change, or discontinuation of antimicrobial therapy.[6,7]

The UK Department of Health and Social Care 5-year action plan for AMR 2024–29 aims to conserve and steward the effectiveness of existing antimicrobials by ensuring that antibiotics are prescribed responsibly and for an optimal duration with timely de-escalation.[8] An approach known as Start Smart Then Focus is recommended for antibiotic prescribing in order to reduce AMR and improve patient safety.[9] The UK National Institute for Health and Care Excellence (NICE) guidance on antimicrobial stewardship[10] recommends reviewing intravenous antimicrobial prescriptions at 48–72 h, including response to treatment and microbiological results, to establish if the antimicrobial needs to be continued and, if so, whether it can be switched to a narrower spectrum antibiotic or an oral antibiotic.[11]

Following a systematic review and cost-effectiveness analysis of procalcitonin testing to guide antibiotic therapy for the treatment of sepsis,[12] NICE recommended further studies to adequately assess the effectiveness of adding procalcitonin algorithms to guide antibiotic treatment in hospitalised adults and children with suspected or confirmed serious bacterial infection. We aimed to assess whether addition of procalcitonin testing to usual care could safely allow a reduction in duration of antibiotic therapy in hospitalised children with suspected or confirmed serious bacterial infection compared with usual care alone. We also assessed the cost-effectiveness of procalcitonin-guided antibiotic treatment compared with usual care for children with suspected or confirmed bacterial infection.

Methods

Study design and participants

The Biomarker-guided duration of Antibiotic Treatment in Children Hospitalised with confirmed or suspected bacterial infection (BATCH) trial was a pragmatic, multicentre, open-label, parallel, two-arm, individually randomised, controlled trial with internal pilot study conducted in paediatric wards or paediatric intensive care units (PICUs) in six children's hospitals and nine district general hospitals in England and Wales. The trial assessed the use of an additional procalcitonin test to guide antimicrobial prescribing decisions. The protocol[13] was approved by the North West–Liverpool East Research Ethics Committee (18/NW/0100) and the UK Health Research Authority.

The study population included all patients aged 72 h to 18 years admitted to hospital who commenced intravenous antibiotics for confirmed or suspected serious bacterial infection and were expected to remain on intravenous antibiotics for more than 48 h. We excluded preterm infants younger than 37 weeks corrected gestational age, children admitted moribund and not expected to survive more than 24 h, and children not expected to survive at least 28 days because of a pre-existing condition. Further exclusion criteria were bacterial meningitis, bacterial endocarditis, or brain abscess, and complicated bone and joint infections. Children who had received antibiotics for surgical prophylaxis, had chronic comorbidities, were severely immunocompromised, or had a high probability of requiring sustained intravenous antibiotics therapy were excluded. Finally, we excluded children with an existing directive to withhold life-sustaining treatment and inborn infants admitted to neonatal intensive care units, neonatal high dependency units, special care baby units, or postnatal wards. The full list of inclusion and exclusion criteria are listed in the appendix (pp 9–10). Eligible participants were identified by the clinical care team, the clinical members of the research team involved in care of children on the ward, or the general paediatric or infectious diseases teams involved in care of children on the ward.

Parents or guardians gave written informed consent for their child to participate in the trial (or the child consented themselves if older than 16 years or Gillick competent). Children with capacity were given the option to sign an age-appropriate assent form in addition to their parent or guardian's consent (copies of the informed consent form and participant information sheet are in the appendix pp 11–20). Where consent was later withdrawn, data were collected up to the point of withdrawal.[13] This trial is registered with the International Standard Randomised Controlled Trial Number registry, ISRCTN11369832.

Randomisation and masking

Patients expected to require intravenous antibiotics for more than 48 h were randomly assigned (1:1) to receive either current clinical management alone (usual care group) or clinical management with the addition of a procalcitonin test guided algorithm (procalcitonin group). Using a secure 24 h web-based randomisation programme controlled centrally by the Centre for Trials Research at Cardiff University (Cardiff, UK), randomisation was by minimisation,[14] with site and age group (0–6 months, 6 months to 2 years, 2–5 years, and older than 5 years) as minimisation factors and a random element to reduce predictability (80% chance of being allocated to the group that minimises covariate imbalance). Details of the age group cutoffs and random element were documented in a separate randomisation protocol and concealed from the treating teams. Due to the nature of the intervention, participants and health-care personnel conducting the test, reviewing the results from the intervention, and assessing outcomes were unblinded to group assignment. All members of the analysis team were blinded to participant group assignment.

Procedures

To guide decisions about antibiotic discontinuation and de-escalation, participants in the usual care group were monitored by routine laboratory tests such as white cell count and C-reactive protein and by clinical examination. In the procalcitonin group, in addition to usual care, blood samples were sent to the hospital laboratory for procalcitonin tests at baseline (randomisation) and every 1–3 days throughout the intravenous antibiotics treatment.

All clinical management decisions were recorded. Local procedures were followed for participants who were discharged home with out-patient parenteral antimicrobial therapy (OPAT). The OPAT nursing team documented antibiotic doses received and sent data electronically to the research team.

Blood samples for procalcitonin tests were analysed on site using a semi-automated immunoassay-based VIDAS platform (bioMérieux, Marcy l'Étoile, France).[13] Assay results were fed into an algorithm with predefined thresholds that had been set from a previous prospective comparison of biomarkers of serious bacterial infection in a heterogeneous cohort of critically ill children with longitudinal biomarker profiles (appendix p 21).[7] The algorithm layout was designed in collaboration with clinicians of the lead recruiting sites and provided both definitive guidelines (eg, stop antibiotics if procalcitonin is <0·25 ng/mL) and advisory guidelines (eg, consider oral switch if procalcitonin concentrations decreased by >80%). Clinicians could over-rule the algorithm according to clinical judgement. Training on interpreting the procalcitonin results and algorithm guidance was provided.

Participant outcome data during treatment were recorded daily (up to and including day 28, or until discharge) by research nurses who also reviewed patient charts and medical notes to collect participant data (appendix pp 22–24).[13] At day 28 (+2 weeks) after

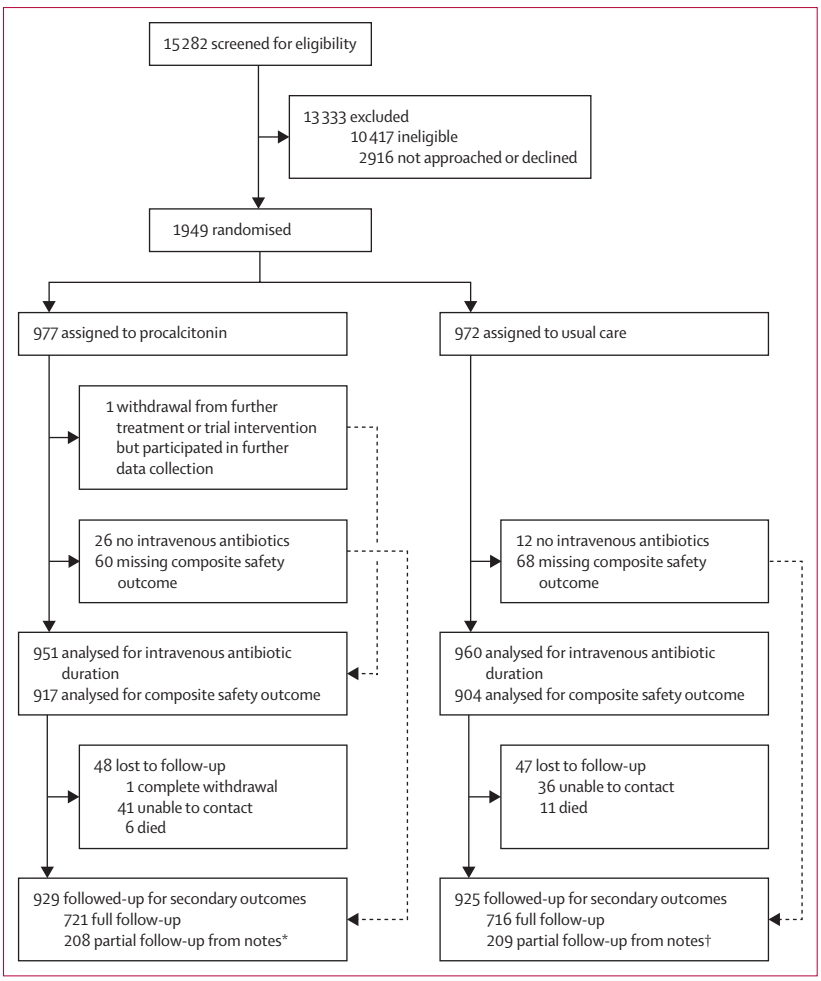

Figure 1: **Trial profile**
*Includes partial withdrawal: four withdrew from active follow-up but allowed existing data and medical records to be used; two withdrew from further treatment or trial intervention and active follow-up and withdrew from questionnaires, but allowed existing data and medical records to be used; and one withdrew from data linkage for future studies. †Includes partial withdrawal: one withdrew from further treatment or trial intervention and active follow-up and withdrew from questionnaires, but allowed existing data and medical records to be used.

discharge, there was a follow-up by telephone or email with the parent or guardian to ask about the health-care use and quality of life of the child. If contact by telephone was unsuccessful, a questionnaire was posted to the parent or guardian for them to complete and return with a prepaid envelope. If the day 28 questionnaire was not returned by the parent or guardian, a minimum dataset was completed from the electronic patient record. Sex data and ethnicity data were collected from patient records.

To assess the effect on health outcomes, participants' utilities were measured using the Child Health Utility 9D (CHU9D), a health-related quality of life measure for children. To assess productivity losses, parents of participants were asked to disclose missed work and school days during their children's hospital stay and up to 28 days following randomisation.

Outcomes

The coprimary outcomes were duration of intravenous antibiotic treatment and a composite safety outcome with three components: (1) unscheduled admissions or readmissions to the PICU with or without infective diagnosis, or unplanned readmission to hospital, within 7 days of stopping intravenous antibiotics; (2) restarting intravenous antibiotic therapy (for any reason) within 7 days of stopping intravenous antibiotics; and (3) mortality (death for any reason) in the 28 days following randomisation.

The secondary outcomes were: each of the three individual components of the composite safety outcome; suspected adverse drug reactions, categorised using the Liverpool Causality Assessment Tool;[15] hospital-acquired infection up to 28 days; total duration of antibiotic use (intravenous and oral), derived from the starting and stopping times of antibiotic use; time to discharge from hospital; and time to switch from broad to narrow spectrum antibiotics. Broad and narrow spectrum antibiotics were defined using a previously published classification.[16]

Specific objectives of the cost-effectiveness analysis were to establish the average cost of a hospital episode and changes in health utility (CHU9D) from baseline to day 28 post-randomisation.

Statistical analysis

The trial was powered based on the two coprimary endpoints to detect both non-inferiority in terms of the composite safety endpoint and superiority in terms of reducing intravenous antibiotic duration. Based on published rates of 15% readmission within 28 days,[17] up to 3% for reinstating intravenous antibiotic therapy, and 3% for mortality,[18–20] and considering some overlaps, around 15% of participants in the usual care group were assumed to have at least one of the safety events included in the composite endpoint. The SAPS trial in adults used an absolute non-inferiority margin of 8% for mortality.[21] Given the lower expected rate of safety outcomes in children than in adults, we chose a similar relative non-inferiority bound of 5%, meaning that an increase in the composite safety outcome from 15% to no more than 20% using procalcitonin-guided therapy would be considered non-inferior. This non-inferiority margin falls within the range reported in a systematic review of absolute and relative non-inferiority margins used in published trials comparing medications in both infectious diseases trials and trials with paediatric patients.[22] With a one-sided significance level of 5% and 90% power, 1748 participants were needed to test non-inferiority for the composite safety outcome. This sample size would also provide 99% power to detect a clinically meaningful 1-day reduction in intravenous antibiotic duration[20] from an estimated median of 5 days in the usual care group,[23] corresponding to a hazard ratio (HR) of 1·25 based on a two-sided significance level of 5%. Assuming independence of the

two coprimary outcomes, this sample size provided at least 89% power for the combined analysis.[24] Anticipating 10% loss to follow-up, the final sample size target was 1942.

The primary analysis sample for each coprimary endpoint included all randomly assigned participants with available outcome data. Logistic regression was used to estimate an adjusted odds ratio for the composite safety outcome, which was then transformed into a risk difference using standardisation. A one-sided 95% CI was constructed via the delta method, as implemented in the Stata command adjrr,[25] to conclude non-inferiority if the upper bound was below the margin of 5% on the risk difference scale or (in a secondary analysis) below the corresponding margin of 1·33 on the relative risk scale.

Cox regression was used to derive a two-sided 95% CI to compare intravenous antibiotic durations with estimates presented by Kaplan–Meier analysis. Trial group and the minimisation factors were included as covariates in the model for each coprimary endpoint, with continuous age as fixed effect and recruiting centre as random effect. The intervention was to be judged successful only if both coprimary endpoint analyses were individually successful (ie, non-inferior safety and reduction of intravenous antibiotic duration), thus not requiring multiplicity correction.[24]

Secondary outcomes were analysed in logistic or Cox regression models, as appropriate, using the same covariate adjustments as in the primary outcome analysis. Exploratory subgroup analyses were performed by infected organ system and recruitment before or after the COVID-19 pause (prespecified) and by recent surgery and whether the recruiting site had an antimicrobial stewardship programme in place (post-hoc). The post-hoc analysis of antimicrobial stewardship-led and non-antimicrobial stewardship-led sites tested whether the intervention would have a bigger impact where antimicrobial stewardship best practice is not yet established, and the post-hoc analysis for recent surgery explored any effect of prophylactic antibiotics used during surgery or post-operative antibiotics for infectious complications after surgery. Regression models with and without subgroup–group interaction terms were compared using a likelihood-ratio test.

Sensitivity analyses included adjusting the non-inferiority margin for deviations from the assumed 15% usual care group risk using a power-stabilising arcsine transformation,[26] and excluding participants found to be ineligible after recruitment. We also performed a supplementary complier average causal effect (CACE) estimation using a two-stage regression approach and bootstrapped CIs to account for non-adherence to the procalcitonin intervention using different definitions.

Our economic analysis adopted an NHS and personal social services perspective in line with NICE guidelines.[27] Costs associated with the procalcitonin test were accounted for along with costs related to health-care provision in a hospital setting, primary care, emergency services, and medicines. A micro-costing approach was used to calculate the costs of the intervention. All costs are presented in British Sterling (£) and updated to 2021 cost figures using the NHS inflation index. Information on the cost of antibiotic prescriptions was obtained from the NHS Electronic Drug Tariff 2023, which contains data regarding the prices paid for specific drugs by NHS Trusts and Health Boards. The cost of antibiotics was deflated to 2021 using gross domestic product deflators. The incremental cost-effectiveness ratio was calculated focusing on a clinically effective outcome that entails a reduction in the number of days on intravenous antibiotics while ensuring equal or enhanced safety outcomes. To address the issue of missing values, a multiple imputation with chained equations approach was used.[28] To account for uncertainty in cost-effectiveness outcomes, a non-parametric bootstrap with 1000 replications was used to derive 95% CIs. Sensitivity analysis was conducted through a complete case analysis.

Stata version 17 was used for statistical analysis and R version 4.3.1 was used for data cleaning and visualisation. A detailed statistical analysis plan has been

	Procalcitonin group (n=977)	Usual care group (n=972)
Age at randomisation, years	3·1 (0·8–8·8)	3·1 (0·7–8·7)
Sex		
Female	427 (44%)	478 (49%)
Male	550 (56%)	494 (51%)
Ethnicity*		
Asian or Asian British	37/939 (4%)	34/923 (4%)
Black, African, Caribbean, or Black British	12/939 (1%)	14/923 (2%)
Mixed or multiple ethnic groups	42/939 (4%)	39/923 (4%)
Other ethnic group	10/939 (1%)	8/923 (1%)
White	838/939 (89%)	828/923 (90%)
Duration of symptoms at admission, h	70 (24–144)	60 (24–120)
Prescribed antibiotic use in past 14 days*	423/972 (44%)	418/970 (43%)
Route of admission*		
Emergency department or acute assessment unit	532/974 (55%)	534/971 (55%)
General practitioner	19/974 (2%)	20/971 (2%)
High dependency unit	34/974 (3%)	29/971 (3%)
Inpatient ward	62/974 (6%)	60/971 (6%)
Other hospital	237/974 (24%)	238/971 (25%)
Paediatric intensive care unit	42/974 (4%)	35/971 (4%)
Operating theatre	48/974 (5%)	55/971 (6%)
Comorbidities*		
None	575/964 (60%)	571/963 (59%)
One	114/964 (12%)	126/963 (13%)
Two or more	275/964 (29%)	266/963 (28%)

Data are median (IQR), n (%), or n/N (%). *Data are not available for all randomly assigned participants.

Table 1: **Baseline characteristics of the randomised participants**

For the **NHS Electronic Drug Tariff** see https://www.drugtariff.nhsbsa.nhs.uk/#/00849298-DD/DC00849294/Home

	Procalcitonin group (n=977)	Usual care group (n=972)
Bone, joint, or muscle infection	86 (9%)	99 (10%)
CNS infection*	5 (1%)	5 (1%)
Fever alone	30 (3%)	28 (3%)
Influenza-like illness	2 (<1%)	8 (1%)
Gastrointestinal or abdominal infection	147 (15%)	128 (13%)
Inflammatory syndrome	3 (<1%)	13 (1%)
Lower respiratory tract infection	213 (22%)	221 (23%)
None	5 (1%)	4 (<1%)
Other	143 (15%)	142 (15%)
Otitis media	5 (1%)	2 (<1%)
Syndromes caused by defined pathogen†	0	2 (<1%)
Sepsis syndrome	129 (13%)	130 (13%)
Soft tissue infection	135 (14%)	113 (12%)
Tonsillitis or pharyngitis	16 (2%)	15 (2%)
Unknown	25 (3%)	32 (3%)
Urinary tract infection	89 (9%)	94 (10%)
Upper respiratory tract infection (other)	38 (4%)	35 (4%)

Data are n (%). Each patient could have zero, one, or multiple initial diagnoses. *Eg, central line infection, line sepsis, culture negative meningitis, enterovirus meningitis, meningococcal meningitis, viral meningitis, and meningoencephalitis. †Eg, measles, varicella, and scarlet fever.

Table 2: **Initial diagnoses by study group**

	Procalcitonin group (n=951)	Usual care group (n=960)	Treatment effect
Median intravenous antibiotic duration, h (IQR)	96·0 (59·5–155·5)	99·7 (61·2–153·8)	HR 0·96 (95% CI 0·87–1·05)
Composite safety outcome	78/917 (9%)	85/904 (9%)	RD –0·81% (95% CI upper bound 1·11); RR 0·90 (95% CI upper bound 1·15)

Data are n/N (%) unless otherwise stated. 95% CIs for the composite safety outcome are one-sided, with no lower bound. Covariates in all models: centre as a random effect and age as a fixed effect. HR=hazard ratio. RD=risk difference. RR=risk ratio.

Table 3: **Coprimary endpoint analysis**

published.[14] The protocol is included in the appendix (pp 35–47). An independent data monitoring committee reviewed accumulating safety data, potential trial intervention benefit, and data quality at least annually.

Role of the funding source

The funder of the study had no role in study design, data collection, data management, data analysis, data interpretation, or writing of the report.

Results

Between June 11, 2018, and Oct 12, 2022 (with a pause in recruitment between March 20 and June 11, 2020 due to the COVID-19 pandemic), 15 282 patients were screened for eligibility, 1949 of whom were enrolled. 977 participants were randomly assigned to receive procalcitonin-guided antibiotic therapy and 972 were randomly assigned to receive usual care (figure 1). 905 (46%) participants were female and 1044 (54%) were male. The main analysis of the coprimary endpoints included 1911 participants with available non-zero intravenous antibiotic durations and 1821 participants with available composite safety data. Participant demographics and baseline characteristics are listed in table 1, and initial diagnoses are listed in table 2.

78 (9%) of 917 participants in the procalcitonin group and 85 (9%) of 904 participants in the usual care group had at least one event covered by the composite safety outcome measure (estimated adjusted risk difference –0·81% [95% CI upper bound 1·11]; table 3). The 95% CI upper bound was less than the non-inferiority margin of 5%, implying non-inferiority of procalcitonin-directed antibiotics therapy to usual care in terms of the composite safety endpoint. The sensitivity analysis using an arcsine-transformed margin of 3·96% (which is more stringent as the observed risk of a safety event was lower than the initially assumed 15%) also showed non-inferiority of procalcitonin-directed antibiotic therapy to usual care. Non-inferiority was also shown on a relative risk scale, with an estimate of 0·90 (95% CI upper bound 1·15), which is less than the relative non-inferiority margin of 1·33.

The median intravenous antibiotic duration was 96·0 h (IQR 59·5–155·5) in the procalcitonin group and 99·7 h (61·2–153·8) in the usual care group (HR 0·96 [95% CI 0·87–1·05]), providing no evidence of a treatment effect on intravenous antibiotic duration (table 3; figure 2).

We also found no evidence of a treatment effect on any secondary outcome (appendix p 25). Likewise, none of the prespecified or post-hoc subgroup analyses showed any significant differences in the treatment effect between subgroups (appendix p 26). No adverse events other than those included in the coprimary safety composite were reported.

Only 226 (24%) of 939 participants in the procalcitonin group were treated strictly in adherence with the protocol (table 4); their median intravenous antibiotic duration was 77·3 h (IQR 50·0–132·0). Records showed that within the procalcitonin group, procalcitonin test results were not considered for about a third of participants, and for another third, test results were not available in time for the first clinical review after randomisation. These findings suggest that the process of obtaining procalcitonin results was an obstacle to implementation. The median number of completed procalcitonin tests per participant was 2 (IQR 1–4); of the total 2551 blood samples analysed, 829 (32%) samples contained less than 0·25 ng/mL procalcitonin, and 1161 (46%) samples contained no more than 0·50 ng/mL procalcitonin.

The sensitivity analysis excluding participants subsequently found to be ineligible showed very similar results to the primary analysis (data not shown). CACE estimates based on the various definitions of non-adherence were mostly consistent with the conclusion of

non-inferior safety and no change in intravenous antibiotic duration (appendix p 27). The CACE estimates emulating a per-protocol analysis (adherence defined as procalcitonin results available and considered by the clinician) showed a risk difference of −3·1% (95% CI upper bound 7·0) for the composite safety outcome and an HR of 0·82 (95% CI 0·56–1·22) for the treatment effect on intravenous antibiotic duration. The point estimates were more strongly in favour of the procalcitonin group in these analyses than in the primary analysis but CIs were wider.

Total costs were higher in the procalcitonin group than in the usual care group, with costs related to hospital stays being the largest component, as is usual in this type of analysis (appendix p 28). Health care use costs after hospital discharge up to 28 days after randomisation did not differ between groups (appendix p 29). Estimated average costs using bootstrapping were higher for participants in the procalcitonin group than in the usual care group for children aged 5 years and older and for all age groups; however, average costs were higher for participants in the usual care group than in the procalcitonin group for children younger than 5 years (appendix p 30).

Clinical and health outcomes, incremental costs, and cost-effectiveness based on imputed datasets, including costs related to health-care resources used within the follow-up period (up to 28 days after discharge), show that the intervention is not cost-effective (appendix pp 31–32). We draw similar conclusions from sensitivity analysis using complete cases (data not shown).

There was no statistically significant difference in CHU9D scores from baseline to 28 days after randomisation between the procalcitonin group and the usual care group (appendix p 33).

Productivity losses were higher in the procalcitonin group than the usual care group, both during the hospital stay and after discharge, up to day 28 after randomisation (appendix p 34). More than 95% of the observations related to travel costs were missing; therefore, those have not been included as part of the direct non-medical costs.

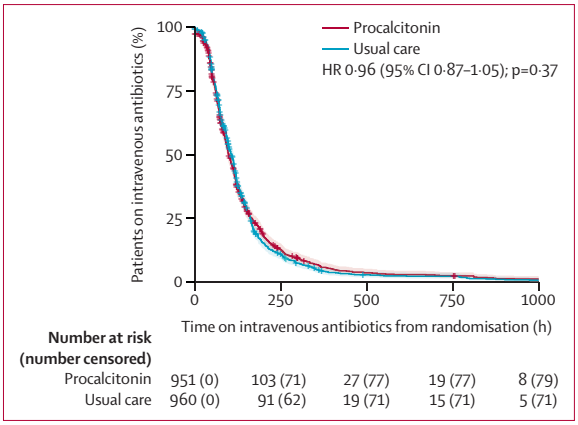

Figure 2: **Kaplan–Meier estimates of the duration of intravenous antibiotic use**
Censored observations shown by + symbols.

	Adherence
Procalcitonin test availability	
At all clinical reviews	360/948 (38%)
At any clinical review	775/948 (82%)
At first clinical review	583/949 (61%)
Procalcitonin test was considered	
At all clinical reviews	226/939 (24%)
At any clinical review	618/928 (67%)
At first clinical review	438/939 (47%)
Algorithm adhered to	
At all clinical reviews	153/940 (16%)
At any clinical review	527/922 (57%)
At first clinical review	352/939 (37%)

Data are n/N (%).

Table 4: **Adherence in the procalcitonin group**

Discussion

A procalcitonin-guided algorithm to guide intravenous antibiotic duration in children hospitalised with suspected or confirmed serious bacterial infection did not reduce intravenous antibiotic duration and was non-inferior to usual care in terms of safety. Our cost-effectiveness analysis concluded that procalcitonin was more costly than usual care and without a significant reduction in intravenous antibiotic duration.

Our findings are inconsistent with those from other multicentre randomised controlled trials in high-income countries, testing procalcitonin-based decision making in three tightly defined patient groups. Procalcitonin-guided decision making was superior to usual care in reducing antibiotic therapy in neonates at low risk with suspected early-onset sepsis;[29] substantially lowered antibiotic exposure and was non-inferior to usual care in acutely ill adults;[30] and increased the rate of antibiotic de-escalation with a reduction of 1·1 days of antibiotic treatment, without adverse outcomes, in children after cardiovascular surgery.[31] In the secondary analysis of the NeoPInS study,[32] C-reactive protein performed slightly better than procalcitonin, but C-reactive protein was part of the definition of uncertain and probable sepsis cases, which might have artificially increased the diagnostic performance of C-reactive protein compared with procalcitonin. Additionally, NeoPInS[32] excluded participants with proven infection, which was not the case in the BATCH study. In a previous observational study, we found that longitudinal profiles for procalcitonin showed the greatest percentage decrease in values over the first 7 days of therapy in children with serious bacterial infection.[7] Adherence to the algorithm at first clinical review was 37%, and 57% at any clinical review, which is similar to the SAPS[21] and PRORATA trials.[30] This implementation challenge emphasises the importance

of behaviour change interventions, training, and feedback to improve adherence in future trials.[33,34]

A systematic review and meta-analysis of hospitalised adult patients reported that procalcitonin-guided antibiotic therapy was shown to be effective and safe in the reduction of antibiotic duration in patients with both sepsis and respiratory tract infections.[35] However, the magnitude of the effect on intravenous antibiotic duration was, at most, 1 day. This reduction is clinically significant if it is in the context of other antimicrobial stewardship measures, such as switching from broad-spectrum to narrow-spectrum antibiotics or avoiding unnecessary antibiotic initiation. A single additional antibiotic treatment day is associated with a 7% absolute increase in risk of resistance.[36] There was no statistically significant difference in the duration of hospitalisation, recurrence of infection or rehospitalisation, or 28-day mortality, but in-hospital mortality was significantly reduced in procalcitonin-guided therapy compared with usual care.[35] This systematic review was in adult patients rather than children. The adherence reported in most studies was higher than in the BATCH trial, although in the SAPS trial,[21] adherence was only 44% at 24 h and 53% at 48 h, and in the PRORATA trial,[30] adherence was 53%. Despite this low adherence, both studies showed a reduction in antibiotic duration with procalcitonin compared with usual care. Of note, the duration of antibiotics in both those trials was substantially higher than the median duration in the BATCH trial; therefore, the potential for procalcitonin, or any other biomarker, to reduce antibiotic duration was limited.

A systematic review and meta-analysis of procalcitonin-guided antibiotic therapy in critically ill adult patients reported that procalcitonin-guided therapy might be associated with reduced antibiotic use and lower 28-day mortality but higher infection recurrence with similar length of stay in the intensive care unit and in hospital.[37]

We propose the following explanations for our findings. First, unlike previous studies and the systematic review of patients with sepsis or respiratory infections mostly in the intensive care unit setting, our study population was very heterogeneous, and included patients in the PICU and in the ward, and patients with a vast range of diagnoses (including pneumonia, urinary tract infection, sepsis, bone or joint infections, and intra-abdominal infections). Procalcitonin might be useful in guiding antibiotic decisions in a carefully selected subgroup of patients, but our study was not powered to show subgroup differences. Second, we used a specific test platform, with restricted access to procalcitonin tests only for the trial, to avoid potential contamination of the control group by making procalcitonin testing available on routine hospital high-throughput laboratory analysers. Although the chosen test platform was an assay that was quick and simple to use, the fact that it did not align to the patient pathway meant that results were not always available at clinical reviews and therefore not being considered in the decision making process. Third, despite site research teams being trained in use of the procalcitonin algorithm, and stickers and credit-card-sized laminates for staff lanyards being produced for use by the clinical teams, adherence to the procalcitonin algorithm was low (36% at first clinical review and 54% at any clinical review). A lack of previous exposure of clinicians to using procalcitonin tests to guide antibiotic decisions might have made it difficult for them to trust the procalcitonin result and adhere to the algorithm. Poor adherence to the algorithm might have undermined its effectiveness in reducing duration of intravenous antibiotics. Fourth, the four lead sites that contributed the most participants (1611 [83%] of 1949) all had dedicated consultant-led paediatric antimicrobial stewardship programmes, conducting antimicrobial stewardship ward rounds at least twice a week.[38] These four sites had already implemented most of the evidence-based and consensus-led recommendations for paediatric antimicrobial stewardship by the time the trial started recruiting.[4]

Our study has several strengths. The study was designed to be pragmatic and therefore represent routine clinical practice in diverse settings, including both smaller general hospitals and large teaching hospitals, and include ethnically diverse and low-income areas in cities and towns. Pragmatic designs allow real-world evaluation of clinical effectiveness, but do not typically focus on implementation processes, which would allow the intervention to be scaled up if found to be effective. An effectiveness-implementation hybrid design allows for the testing of effectiveness of the intervention while observing and gathering information on implementation of the intervention to optimise fidelity.[39] We used coprimary outcomes that considered both effectiveness and safety to ensure that participants were not harmed in the promotion of antimicrobial stewardship. A cost-effectiveness analysis is important to show that regardless of whether the intervention is clinically effective, it might or might not have potential to improve health-care system value.

Limitations of the study are that robust antimicrobial stewardship programmes were already implemented in the lead recruiting sites, and that adherence to the algorithm was poor. Possible consequences of low adherence include falsely claiming non-inferiority with respect to the safety outcome[40] and failure to detect effectiveness with respect to antibiotic use.

Our findings provide evidence that procalcitonin-guided algorithms do not reduce duration of antibiotic treatment in hospitalised children already on intravenous antibiotics; however, the study does not address whether procalcitonin use reduces antibiotic initiation in children presenting to the emergency department. The PRONTO trial,[41] which recently completed recruitment of more than 7000 adult patients with suspected sepsis presenting to the emergency department, will evaluate whether a procalcitonin-guided risk assessment can lead to

a reduction in intravenous antibiotic initiation, and the ADAPT-Sepsis trial[42] will evaluate whether a treatment protocol based on monitoring C-reactive protein or procalcitonin safely reduces antibiotic duration in hospitalised adults with sepsis.

Future studies of biomarker-guided interventions should use adaptive platform trial designs embedded in routine clinical care to comprehensively evaluate multiple diagnostic tests, to establish clinical utility, safety, cost-effectiveness, and implementation outcomes robustly and rapidly. A better understanding of the complex interactions influencing whether, how, and why clinicians act on information from diagnostic tests to make antibiotic prescribing decisions will improve trial intervention fidelity and facilitate implementation and adoption of tests shown to be effective. Antimicrobial stewardship is a multicomponent health service activity, influenced by a range of interdisciplinary, organisational, service-level, professional, individual, and behavioural factors,[43] and future trials must build in comprehensive exploration of this hidden complexity to ensure the success of future implementation. Diagnostic stewardship demands that tests are performed at the right point in the clinical pathway, on the right patients, in the right way, with results interpreted correctly, to improve clinical decisions about severe infection.

Our results suggest that in hospitalised children treated with intravenous antibiotics for suspected or confirmed serious bacterial infection, a procalcitonin-guided algorithm is not effective in reducing intravenous antibiotic duration, especially where robust antimicrobial stewardship programmes are already implemented. Implementation frameworks are required to ensure intervention fidelity in biomarker-guided trials.

Contributors

LB-H, JB, SNF, LH, CH, KH, CM, SCP, SP, CVEP, JP, ET-J, and EDC conceived, designed, and obtained funding for the trial. All authors oversaw trial conduct and management, and contributed to acquisition, analysis, and interpretation of the data. DH, PP, SS, CM, and HX directly accessed and verified the data, and conducted the analyses. C-AW, PP, CM, HX, and EDC drafted the manuscript. All authors had access to the data, critically revised and approved the manuscript for submission, and had final responsibility for the decision to submit for publication.

Declaration of interests

EDC was a member of the National Institute of Health and Care Research (NIHR) Invention for Innovation panel (November, 2011–23), the NIHR Diagnostic Advisory Committee (April, 2014–September, 2020), Medical Research Council Developmental Pathway Funding Scheme panel (March, 2020–23), and Medical Research Council COVID-19 Agile panel (July 2020–21), and is funded by the National Institute of Health and Care Research (NICE) NIHR Senior Investigator award. SNF is a member of the NIHR Health Technology Assessment (HTA) Commissioning Committee, was Chair of UK NICE Sepsis (2014–16) and Lyme Disease Guidelines (adult and children; 2016–18), and is funded by the NIHR Senior Investigator award. KH is Deputy Chair of the NIHR Research Processors panel, is a member of the NIHR HTA Funding Committee Policy group, and was a member of the NIHR HTA General Committee (2016–22). PP is a member of the NIHR Efficacy and Mechanism Evaluation Committee. CVEP is chair of the ELVIS kids study trial steering committee and the EASY study independent data monitoring committee. HMN is jointly funded by the UK Medical Research Council and the European Union EDCTP2 programme. All other authors declare no competing interests.

Data sharing

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

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