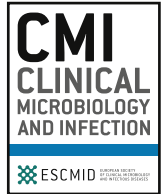




Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original Article

Early switch to oral antibiotic therapy in patients with low-risk neutropenic sepsis (EASI-SWITCH): a randomized non-inferiority trial

Vicky Coyle¹, Caroline Forde¹, Danny F. McAuley², Richard H. Wilson³, Mike Clarke^{4,5}, Ruth Plummer⁶, Margaret Grayson⁷, Cliona McDowell⁵, Ashley Agus⁵, Annmarie Doran⁵, Anne L. Thomas⁸, Rosemary A. Barnes⁹, Richard Adams^{9,10}, Ian Chau¹¹, Dawn Storey¹², Ronan McMullan^{2,*}, on behalf of the EASI-SWITCH Investigators

¹ Patrick G Johnston Centre for Cancer Research, Queen's University Belfast, Belfast, UK

² The Wellcome Wolfson Institute for Experimental Medicine, Queens University Belfast, Belfast, UK

³ Translational Research Centre, University of Glasgow, Glasgow, UK

⁴ Northern Ireland Methodology Hub, Queen's University Belfast, Belfast, UK

⁵ Northern Ireland Clinical Trials Unit, Belfast Health and Social Care Trust, Belfast, UK

⁶ Translational and Clinical Research Institute, Newcastle University, Newcastle, UK

⁷ Northern Ireland Cancer Research Consumer Forum, Belfast, UK

⁸ Leicester Cancer Research Centre, University of Leicester, Leicester, UK

⁹ Cardiff University School of Medicine, Centre for Trials Research, Cardiff, UK

¹⁰ Velindre NHS Trust, Department of medical oncology, Cardiff, UK

¹¹ The Royal Marsden NHS Foundation Trust, Gastrointestinal and lymphoma unit, London, UK

¹² The Beatson West of Scotland Cancer Centre, Department of medical oncology, Glasgow, UK

ARTICLE INFO

Article history:

Received 25 April 2023

Received in revised form

19 July 2023

Accepted 22 July 2023

Available online xxx

Editor: L. Scudeller

Keywords:

Antibiotic

Febrile neutropenia

Neutropenic sepsis

Oral

ABSTRACT

Objectives: To determine whether early switch to oral antibiotic treatment in adults with neutropenic sepsis at low risk of complications is non-inferior to switching later.

Methods: This non-inferiority, parallel-group, randomized, open-label clinical trial enrolled UK adults hospitalized with neutropenic sepsis. Participants were randomly assigned to either switch to oral ciprofloxacin plus co-amoxiclav within 12–24 hours or to continue intravenous treatment for at least 48 hours. The primary outcome was a composite measure of treatment failure, 14 days after randomization. The non-inferiority margin was 15%.

Results: There were 129 participants from 16 centres and 125 were assessed for the primary outcome. Of these, 113 patients completed protocolized treatment and comprised the per-protocol population. In total, 9 (14.1%) of 64 patients in the standard care arm met the primary end point, compared with 15 (24.6%) of 61 in the early switch arm, giving a risk difference of 10.5% (1-sided 95% CI, $-\infty$ to 22%; p 0.14). In the per-protocol population, 8 (13.3%) of the 60 patients in the standard care arm met the primary end point, compared with 9 (17%) of 53 in the intervention arm giving a risk difference of 3.7%

The EASI-SWITCH Investigators: Audrey Fenton, Ruth Boyd, Elizabeth Andrzejewski, Theresa Beaver, Noor Haris, Sarah Osborne, Amanda Henderson, Jonathan Stoddart, Hilary Williams, Karen Davies, Kate Beattie, Khurum Khan, Sejal Jain, Lois Mulholland, Jennifer Foreman, Effie Grand, Sarah Salisbury, Luke Nolan, Elizabeth Happle, Sonali Dasgupta, Jackie McGee, Patricia Kane, Sarah Buckley, Iva Damyanova, Joyce Thompson, Daniel Lenton, Mike Smith-Howell, Nicole McKee, Becky Hary, Amanda Holdsworth, Bartlomej Kurec, Amelie Harle, Rachel Barnsley, Louise Heckford, Jeff Neilson, Karen Pearson, Angela Watts, Fharat Raja, Chloe Van Someren, Pauline Leonard, Kayleigh Gilbery, Ceri Powell, Nina Viney

* Corresponding author. Ronan McMullan, Wellcome Wolfson Institute for Experimental Medicine, Queens University Belfast, 97 Lisburn Road, Belfast BT9 7BL, UK.

E-mail address: r.mcmullan@qub.ac.uk (R. McMullan).

<https://doi.org/10.1016/j.cmi.2023.07.021>

1198-743X/© 2023 The Author(s). Published by Elsevier Ltd on behalf of European Society of Clinical Microbiology and Infectious Diseases. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Please cite this article as: Coyle V et al., Early switch to oral antibiotic therapy in patients with low-risk neutropenic sepsis (EASI-SWITCH): a randomized non-inferiority trial, *Clinical Microbiology and Infection*, <https://doi.org/10.1016/j.cmi.2023.07.021>

Randomized controlled trial
Treatment

(one-sided 95% CI, $-\infty\%$ to 14.8%; p 0.59). Duration of hospital stay was shorter in the intervention arm (median 2 [inter-quartile range (IQR) 2–3] vs. 3 days [IQR 2–4]; p 0.002).

Discussion: Although non-inferiority of early oral switch was found in the per-protocol population, the intervention was not non-inferior in the intent-to-treat population. **Vicky Coyle, *Clin Microbiol Infect* 2023;■:1**

© 2023 The Author(s). Published by Elsevier Ltd on behalf of European Society of Clinical Microbiology and Infectious Diseases. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Introduction

Neutropenic sepsis (NS) is a well-recognized complication of systemic anti-cancer treatment (SACT) and requires time-critical management [1–5]. There is less consensus on subsequent management, including timing of the switch from intravenous (i.v.) to oral antibiotic, antibiotic duration and need for hospital admission [6].

Guidance from the UK National Institute for Health and Care Excellence (NICE) recommends switch to oral antibiotics in patients who are at low risk of complications after 48 hours of i.v. therapy [2]. The NICE guideline development group noted that earlier oral switch may be beneficial for patients, but required further research [2]. Current treatment strategies probably drive overtreatment [7].

The EASI-SWITCH trial was designed in response to a commissioned call from the UK National Institute of Health and Care Research Health Technology Assessment programme to address this evidence gap. The trial was terminated before reaching the target sample size because of under-recruitment.

Methods

Study design and inclusion criteria

The protocol has been published [8] and the full trial protocol is provided in Supplementary material. The protocol was approved by a UK Research Ethics Committee (6 October 2015, Ref 15/NI/0161), the study Sponsor (Belfast Health & Social Care Trust), and the research governance oversight group at each participating site. Written informed consent was obtained from all patients. The results are reported in accordance with the CONSORT statement extension for Non-inferiority and Equivalence Trials [9].

This was a multicentre open-label, parallel-group, randomized trial of early switch to oral antibiotics vs. standard care in adult patients presenting with NS following SACT who were at low risk of complications (based on the Multinational Association of Supportive Care in Cancer [MASCC] score). Patients (>16 years) receiving SACT and presenting with neutropenia (absolute neutrophil count of $\leq 1.0 \times 10^9/L$) and either a temperature of at least 38°C or other findings consistent with clinically significant sepsis were eligible for inclusion provided there was: anticipated neutropenia duration of <7 days; MASCC score of ≥ 21 ; adequate oral intake; adequate organ function (transaminase levels of $< 5 \times$ upper limit of normal and creatinine $< 3 \times$ upper limit of normal); and the physician in charge of patients' care agreed with enrolment, including willingness to not prescribe treatment with colony-stimulating factor (CSF).

Patients had to be randomly assigned within 24 hours of starting routine empirical antibiotic treatment (meropenem or piperacillin-tazobactam) for the presenting episode of NS. Exclusion criteria included allergy or contraindication to any study drug; diagnosis of acute leukaemia or haematopoietic stem cell transplant; hypotension within 24 hours pre-randomization (systolic pressure of <90 mmHg or reduction of >40 mmHg from baseline on >1

measurement); previous trial enrolment; previous documentation of a resistant organism; localizing signs of severe infection; unable to provide informed consent; pregnancy; or breastfeeding. Treatment with CSF for the presenting episode excluded otherwise eligible participants, but prophylactic CSF was not an exclusion criterion if prescribed as an integral component of SACT.

Study population, randomization, masking, and stratification

Patients were recruited from 16 UK hospitals (see Supplementary material). Eligible participants were allocated to intervention or standard care arms using an automated online randomization system, ensuring allocation concealment, in a 1:1 ratio with blocks of randomly permuted sizes. Patients, physicians, and investigators were not blinded to treatment after randomization. There were no factors for stratification.

Intervention and follow-up

Patients allocated to control received at least 48 hours i.v. antibiotics (meropenem or piperacillin-tazobactam), in accordance with UK guidelines [2]. Thereafter, oral switch and/or antibiotic discontinuation was at the treating physician's discretion. Patients allocated to intervention received 12 to 24 hours of i.v. antibiotics followed by switch to an oral regimen of ciprofloxacin 750 mg twice daily and co-amoxiclav 625 mg 3 times daily to complete 5 days' total treatment. Additional antibiotics or CSF for treatment of NS were prohibited.

Patients were followed up for 28 days after randomization.

Outcomes

The primary outcome was treatment failure, a composite measure assessed on day 14, defined by the presence of any one of persistence or recurrence of fever (temperature of $> 38^\circ C$) 72 hours after starting i.v. antibiotics; physician-directed escalation from protocol-specified treatment; hospital readmission (related to infection or antibiotic treatment, as assessed by treating physician); critical care admission; or death.

The following secondary outcome measures were also assessed on day 14: (a) time to resolution of fever from initial i.v. antibiotic administration; (b) adverse events because of antibiotics or route of administration; (c) length of hospitalization; and (d) patient preferences for antibiotic treatment (see Supplementary material). Further secondary outcome measures were assessed on day 28 (Table 5).

Results

Demographic and clinical characteristics of patients

Between December 2015 and November 2019, 827 patients were screened, of whom 129 (15.6%) were randomly assigned. The

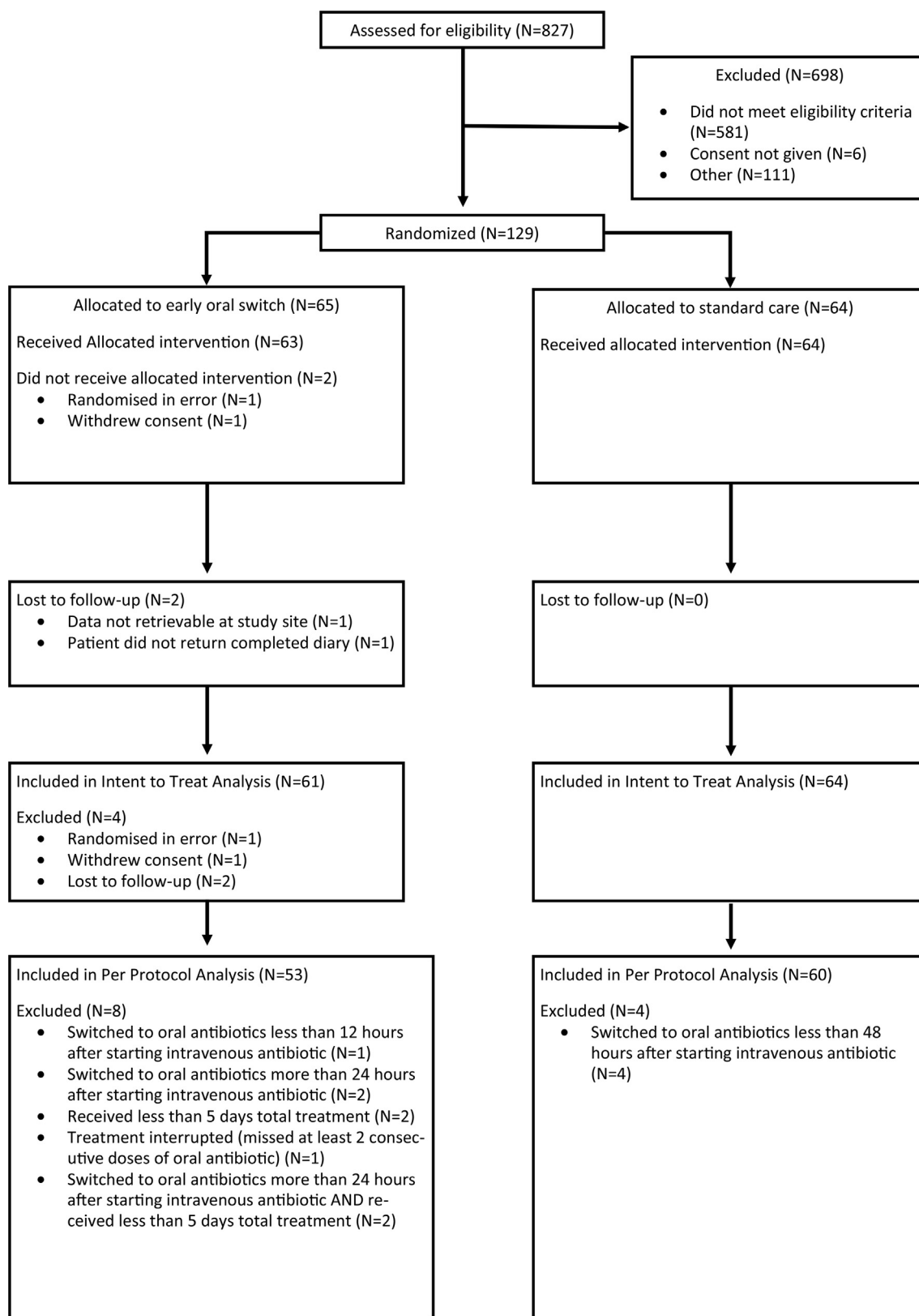


Fig. 1. Study flow diagram.

main reasons for non-randomization after screening were the absence of an absolute neutrophil count $\leq 1.0 \times 10^9/L$, and falling, with a temperature $\geq 38^\circ C$ ($N = 301$); absence of documented fever

$\geq 38^\circ C$ or other signs/symptoms of sepsis ($N = 108$); underlying diagnosis of acute leukaemia ($N = 38$); MASCC score ≤ 21 ($N = 28$); and ongoing treatment with CSF ($N = 25$).

Table 1
Summary demographic and clinical characteristics at randomization

Baseline characteristics	Treatment group	
	Standard care	Intervention
	n = 64	n = 65
Age (y)	56.2 (15.1)	56.6 (13.4)
Gender		
Men	21 (32.8%)	20 (30.8%)
Women	43 (67.2%)	45 (69.2%)
Malignancy		
Solid tumour	59 (92.2%)	62 (95.4%)
Haematological	5 (7.8%)	3 (4.6%)
Solid tumour type	n = 59	n = 62
Breast	30 (50.9%)	36 (58.1%)
Lung	4 (6.8%)	3 (4.8%)
Gastrointestinal/hepatobiliary	4 (6.8%)	5 (8.1%)
Germ cell	3 (5.1%)	0 (0.0%)
Genitourinary	5 (8.5%)	5 (8.1%)
Head and neck	2 (3.4%)	0 (0.0%)
Gynaec	4 (6.8%)	3 (4.8%)
Sarcoma	4 (6.8%)	4 (6.5%)
Other	3 (5.1%)	6 (9.7%)
Cancer treatment intention		
Radical	9 (14.1%)	3 (4.6%)
Palliative	16 (25.0%)	20 (30.8%)
Adjuvant/neoadjuvant	38 (59.4%)	30 (61.5%)
Other	1 (1.6%)	2 (3.1%)
Cancer treatment line	n = 64	n = 64
1st line	54 (84.4%)	55 (85.9%)
2nd line	7 (10.9%)	7 (10.9%)
3rd line and beyond	3 (4.7%)	2 (3.1%)
Maximum temperature	38.2 (0.6)	38.2 (0.8)
Absolute neutrophil count	0.3 (0.3)	0.3 (0.3)
Symptoms of mild local infection ^a		
Cough	15 (23.4%)	21 (32.3%)
Sore mouth/throat	29 (45.3%)	22 (33.8%)
Dysuria	3 (4.7%)	5 (7.7%)
Nausea/vomiting	11 (17.2%)	10 (15.4%)
Diarrhoea	10 (15.6%)	9 (13.9%)
Other symptoms	32 (50.0%)	29 (44.6%)
MASCC score	24.0 (1.8)	24.3 (1.8)
Prophylactic GCSF administered		
Yes	22 (34.4%)	10 (15.6%)
No	42 (65.6%)	54 (84.4%)
C-reactive protein (mg/L)	48.6 (49.2)	50.3 (52.7)
Blood cultures ^b		
Positive	20 (10.9%)	16 (7.6%)
Negative	163 (89.1%)	196 (92.5%)

Measurements recorded on the day of randomization.

Mean (SD) presented for continuous variables and n (%) for all categorical variables. GCSF, Granulocyte colony stimulating factor; MASCC, Multinational Association of Supportive Care in Cancer.

^a Yes responses tabulated.

^b Number of positive blood culture sets; some patients reported >1 of each.

Of the 129 randomly assigned participants, 125 were included in the primary analysis with 4 excluded: 1 randomized in error, 1 withdrew consent, and 2 lost to follow-up. Of the 125 patients, 61 were allocated to the early oral switch arm and 64 to the standard care arm (Fig. 1). Baseline demographic and clinical details of patients are summarized in Table 1 (detailed characteristics in Supplementary materials). The groups were generally balanced across these characteristics.

Trial recruitment was slow despite efforts to maximize recruitment. Following Data Monitoring Committee (DMC) review after 42 months of recruitment (including a 6-month recruitment pause during the 48-month study period), with 129 patients enrolled, the DMC advised the Trial Steering Committee and

Table 2
Analyses for the primary outcome in the intent-to-treat and per-protocol populations

	Standard care	Intervention	Risk difference (One-sided 95% CI)	p
Treatment failure ITT (N = 125)				
Yes	9 (14.1%)	15 (24.6%)	0.105 (−∞ to 0.22)	0.14
No	55 (85.9%)	46 (75.4%)		
Treatment failure PP (N = 113)				
Yes	8 (13.3%)	9 (17.0%)	0.036 (−∞ to 0.148)	0.59
No	52 (86.7%)	44 (83.0%)		

The 95% one-sided confidence limit that was compared with the 15% margin to assess non-inferiority was derived from the upper bound of a two-sided 90% CI. The p value given is from significance testing of observed differences between trial arms using the Pearson chi-square test.

ITT, intention-to-treat; PP, per-protocol.

Sponsor to close the trial. The DMC had full access to study results and, although there were no safety concerns, deemed that reaching the planned sample size of 230 was unachievable.

Primary outcome

In the ITT analysis, 9 (14.1%) of 64 patients in the standard care arm met the treatment failure primary end point, compared with 15 (24.6%) of 61 in the early oral switch arm. The risk difference of 10.5% (one-sided 95% CI, −∞% to 22%; p 0.14) was such that the intervention was not found to be non-inferior to standard care in the ITT population (Table 2).

The result of the PP analysis was not consistent with this. In the PP population, 8 (13.3%) of 60 patients in the standard care arm met the primary end point of treatment failure, compared with 9 (17%) of 53 in the early oral switch arm. The risk difference of 3.7% (one-sided 95% CI, −∞% to 14.8%; p 0.59) was such that intervention was found to be non-inferior to standard care in the PP population.

Of the 12 ITT patients who were excluded from the PP population, 8 had been allocated to the intervention arm; of these, 4 had their antibiotic treatment stopped prematurely, 1 had substantial interruption to treatment (at least 2 consecutive missed doses), and 1 had less than 12 hours of initial i.v. treatment. Among these 8 participants, 6 had treatment failure. The 4 patients excluded from the standard care arm had oral switches after less than 48 hours of i.v. antibiotics.

The main constituents of the composite primary outcome measure that accounted for treatment failure were persistence/recurrence of fever and/or physician-directed escalation from the protocolized antibiotic regimen (Table 3). Critical care admission or death did not account for treatment failure in either arm. Subgroup analyses of the primary outcome in the ITT population found no significant interactions (Table 4).

Secondary outcomes

For patients with available secondary outcome data, the duration of hospital stay was significantly shorter among patients in the intervention arm (median 2 [IQR 2–3] vs. 3 [IQR 2–4] days, p 0.002). There were no statistically significant differences between trial arms for other measures (Table 5). The mean duration of i.v. antibiotic therapy (and SD) was 54.8 hours (24.2) and 22.6 hours (26.9) in the standard care and early switch intervention groups, respectively.

Table 3
Constituents of the composite primary outcome measure leading to patients reaching the treatment failure end point in the ITT population

	Standard care (n = 64)	Intervention (n = 61)	Difference (95% CI)	p
Persistence/recurrence of fever (temperature $\geq 38^\circ\text{C}$) after 72 h of intravenous antibiotic initiation	n = 62	n = 60	0.102 (0.010, 0.215)	
Yes	4 (6.5%)	10 (16.7%)		
No	58 (93.6%)	50 (83.3%)		0.08
Physician-directed escalation from protocol-specified antibiotic treatment				
Yes	6 (9.4%)	10 (16.4%)	0.070 (0.047, 0.187)	
No	58 (90.6%)	51 (83.6%)		0.24
Day 14: critical care admission ^a	n = 62			
Yes	0	0		
No	62 (100%)	61 (100%)		
Day 14: readmission to hospital	n = 62	N = 61	0.001 (0.062, 0.063)	
Yes	2 (3.2%)	2 (3.3%)		
No	60 (96.8%)	59 (96.7%)		0.99
Day 14: patient survival status ^b				
Alive	64 (100%)	61 (100%)		
Deceased	0	0		

The number of patients for whom each component of the composite outcome measure was available is expressed, by the trial arm, for that measure and the p value given is from significance testing of observed differences between trial arms using the Pearson chi-square test.

Frequency and percentage presented for treatment arms.

ITT, intention-to-treat.

^a There were no critical care admissions recorded before day 14.

^b There were no deaths recorded before day 14.

Table 4
Subgroup analyses

	Treatment failures			Interaction p
	Standard care	Intervention	Risk difference (99% CI)	
Neutrophil count at randomization				
$\leq 0.5 \times 10^9/\text{L}$ (n = 92)	7 (14.6%)	11 (25.0%)	0.10 (-0.11 to 0.32)	0.51
$> 0.5 \times 10^9/\text{L}$ (n = 33)	2 (12.5%)	4 (23.5%)	0.11 (-0.23 to 0.45)	
Maximum temperature on presentation				
$\leq 38^\circ\text{C}$ (n = 41)	3 (13.0%)	4 (22.2%)	0.09 (-0.22 to 0.40)	0.50
$\geq 38^\circ\text{C}$ (n = 84)	6 (14.6%)	11 (25.6%)	0.11 (-0.11 to 0.33)	
Positive blood culture				
No (n = 99)	7 (13.7%)	11 (22.9%)	0.09 (-0.11 to 0.29)	0.39
Yes (n = 21)	2 (20.0%)	4 (36.4%)	0.16 (-0.33 to 0.66)	

Risk differences and 99% CI from the treatment \times subgroup interaction models are presented for two of the three pre-specified subgroups and one post hoc subgroup (positive blood cultures at baseline) for the primary outcome of treatment failure. The p values presented are from a global test for interaction and indicate no significant interactions.

Table 5
Secondary outcome measures

	Standard care	Intervention	p
Day 14: time to fever resolution from initial i.v. antibiotic administration (median, interquartile range) ^a	n = 36 25.6 h (8.5 to 46.0)	n = 37 18.5 (9.5 to 39.6)	0.52
Day 14: length of hospital stay (median, interquartile range) ^a	n = 58 3 d (2 to 4)	n = 52 2 d (2 to 3)	0.002
Day 28: readmission to hospital (related to infection or antibiotic treatment) ^b	n = 64 6 (9.4%)	n = 61 11 (18.0%)	0.16
Day 28: change in subsequent planned SACT ^b	n = 61 22 (36.1%)	n = 59 22 (37.3%)	0.89
Day 28: survival ^b	n = 62 61 (98.4%)	n = 61 58 (95.1%)	0.30

The number of patients for whom each secondary outcome measure was available is expressed, by the trial arm, for that measure.

Frequency and percentage presented for treatment arms.

i.v., intravenous; SACT, systemic anti-cancer treatment.

^a Median and interquartile range presented and p value from Wilcoxon rank-sum test.

^b p value from Pearson chi-square test.

A post hoc exploratory analysis using generalized estimating equations found no statistically significant difference in risk of treatment failure, when accounting for possible clustering of observations within study sites (risk difference 10.6 [95% CI, -3.2 to 54.4; p 0.13]).

Adverse events

In total 106 adverse events were recorded until day 14. Overall, 29 serious adverse events were reported. Twelve serious adverse events occurred in the intervention arm. Details are provided in

Supplementary material. In 28 days of follow-up, 3 patients (4.9%) died who were allocated to the intervention arm as compared with one patient (1.6%) in the standard care arm; no deaths occurred within the first 14 days.

Patient preferences

A total of 114 patients (60 standard care; 54 intervention) provided responses to the questionnaire (for full results, see Supplementary material). At least 95% of respondents in each arm were satisfied with care received, the level of hospital support, and their mode of treatment delivery.

A greater proportion in the intervention arm considered it 'important' to be discharged 1 to 2 days earlier, (59% intervention vs. 35% control). However, the majority in both arms accepted risk of readmission with early discharge (72% intervention; 65% control). When presented with the hypothetical scenario of early oral switch and discharge with a possible readmission risk increase (from 1530%), 74% and 64% of intervention and standard care patients, respectively, still preferred early discharge.

Discussion

This trial did not deliver a decisive conclusion on the non-inferiority of early oral antibiotic switch in patients diagnosed with cancer receiving treatment for low-risk NS, perhaps because under-recruitment led to the analysis being underpowered. Although non-inferiority of early oral switch was found in the PP population, analysis of the ITT population was inconclusive.

Although analysis of either population alone may lead to bias, there is particular concern that ITT analysis is not conservative in non-inferiority trials [10,11]. Our findings do not reflect that concern but underscore the potential for inconsistent results arising from analyses of different patient populations. We determined *a priori* that a firm conclusion on non-inferiority of the intervention would be reached only if both ITT and PP analyses agreed.

It is notable that the PP analysis excludes many more patients who had treatment failure in the intervention arm than in the standard care arm. Therefore, because the ITT population included these patients who did not receive the complete protocolized intervention, the ITT analysis risks underestimating the efficacy of the intervention; by comparison, the PP analysis may overcome this issue. Conversely, there is a risk that PP analyses may be associated with bias related to under-inclusion of early treatment failures, although that did not seem to arise in this trial.

Although the 15% non-inferiority margin may appear wide, it should be considered in the manifestation of treatment failure which, in low-risk patients, typically results in fever recurrence and/or treatment escalation to i.v. therapy. In planning the trial, surveys of both medical professionals and patient representatives regarded the margin favourably. Importantly, the patients recruited to this trial affirmed their acceptance of the possible need for re-treatment following early oral switch, corresponding to a margin of this size.

High-quality clinical trial evidence addressing the efficacy and safety of oral antibiotic treatment for NS is limited, relative to the substantial pertinent patient population. Several systematic reviews and meta-analyses have been published focusing on outcome measures of treatment failure and death. Treatment failure is defined inconsistently across individual trials; furthermore, short-term mortality is not a sensitive indicator of treatment effectiveness. Many trials included children and there was considerable heterogeneity in antibiotic regimens. The NICE guideline that led to commissioning of the present trial considered the evidence assimilated within a 2004 Cochrane review as low quality [12].

The Cochrane review was updated in 2013 capturing a further 6 trials (372 patient episodes), reporting a total of 3142 NS episodes from 2372 patients [12]. This review found the relative risk of treatment failure with oral vs. i.v. antibiotics was 0.96 (95% CI, 0.86–1.06). Of 14 trials that recruited adults, data from 1794 patients were included; 12 trials compared upfront oral with i.v. treatment, and the remaining 2 evaluated oral switch at 3 and 6 days, respectively [12]. Most trials were small and typically single centre, with only 2 trials recruiting more than 200 patients [13,14]; one of these evaluated an intervention involving oral switch after at least 3 days of i.v. treatment, more closely representing current standard care than early oral switch [14].

Limitations

The trial did not reach the planned sample size of 230 patients because of slow recruitment. This problem is commonly encountered in supportive care trials in cancer, including previous NS trials. Anecdotally, it seemed that low recruitment was driven by the short time available for randomization following acute unplanned admission (<24 hours). The resulting loss of power may explain the inconclusive nature of the ITT analysis, limiting the opportunity to reach a decisive conclusion for the trial, overall.

Treating physician agreement was a requirement for trial enrolment which has the potential to introduce selection bias. Although allocation concealment was achieved, the open-label nature of the trial raises risk of performance bias. Non-blinded outcome assessment also presents a risk of detection bias with the potential for subjectivity in some components of the composite outcome, although it is not possible to attach directionality to this risk of bias.

Although the high screening:recruitment ratio may impact the applicability of the trial's findings to future patients, most screening 'failures' were because of not meeting inclusion criteria. Therefore, these are most likely to reflect patients who were excluded because they would not meet an acceptable, standardized, definition of NS despite being treated on NS pathways.

It is also recognized that many patients with fever in the setting of neutropenia may not have bacterial infections; as such, antibiotic interventions may not modify their clinical progress. It is often unclear which patients have bacterial infection, even in retrospect, hence the pragmatic nature of this clinical effectiveness trial which was intended to reflect common medical practice.

Conclusion

The trial did not deliver a decisive conclusion on the non-inferiority of early oral antibiotic switch in patients diagnosed with cancer receiving treatment for low-risk NS. Although non-inferiority of early oral switch was found in the PP population, the intervention in the ITT population was not found to be non-inferior. Insufficient power arising from under-recruitment may have contributed to this. The trade-off between early switch, enabling early discharge, and the risk of treatment failure was acceptable to patients.

Author contributions

VC contributed to the concept and design of the trial, funding acquisition, protocol development, recruitment, trial management, data analysis, and manuscript writing. CF contributed to trial design, protocol development, day-to-day trial management, and manuscript writing. RA contributed to funding acquisition, trial design, protocol development, patient recruitment, and manuscript writing. RP contributed to funding acquisition, trial design, protocol

development, patient recruitment, and manuscript writing. AA contributed to funding acquisition, trial design and development, data analysis, and manuscript writing. RAB contributed to funding acquisition, trial design, protocol development, and manuscript writing. IC contributed to funding acquisition, trial design, protocol development, patient recruitment, and manuscript writing. MC contributed to funding acquisition, trial design, protocol development, and manuscript writing. AD contributed to protocol development and study set-up and was responsible for trial coordination and day-to-day management. MG contributed to funding acquisition, trial design, trial development and management, review of patient-facing materials, and lay communication. DFM contributed to funding acquisition, trial design, protocol development, and interpretation of results. CM contributed to protocol development, statistical methodology, data analysis, interpretation of results, and manuscript writing. NH contributed to patient recruitment, day-to-day trial management, and manuscript writing. DS contributed to funding acquisition, trial design, protocol development, patient recruitment, and manuscript writing. ALT contributed to funding acquisition, trial design, protocol development, patient recruitment, and manuscript writing. RHW contributed to funding acquisition, trial design, protocol development, patient recruitment, and manuscript writing. RM contributed to the concept and design of the trial, funding acquisition, protocol development, trial management, data analysis, and manuscript writing.

Transparency declaration

Conflict of interest

VC reports NIHR Health Technology Assessment Programme commissioned research grant institutional funding to deliver the trial (Ref 13/140/05) and a Cancer Research UK Doctoral Fellowship research grant that part-supported this submitted work. She also reports research grants from Cancer Research UK, the Northern Ireland Public Health Agency, and Astex Pharmaceuticals (UK) as well as personal fees from Merck Sharpe & Dohme Ltd (MSD, UK) and personal fees and non-financial support from Servier Laboratories (France) for attending educational meetings, all unrelated to the submitted work. She reports membership of the NIHR Efficacy and Mechanisms (EME) Funding Committee and acting as Executive Chair of the NIHR Cancer and Nutrition Collaboration. RA reports NIHR Health Technology Assessment Programme commissioned research grant institutional funding to deliver the trial (Ref 13/140/05). He also reports research grants from Astra-Zeneca plc (UK) and Merck Sharpe & Dohme Ltd (MSD, UK) as well as personal fees from Bayer Pharmaceuticals (Germany), Amgen Inc (USA) & Servier Laboratories, and non-financial support for attending meetings from Amgen Inc, Servier Laboratories and Merck Serono (Switzerland), all unrelated to the submitted work. AA reports NIHR Health Technology Assessment Programme commissioned research grant institutional funding to deliver the trial (Ref 13/140/05). She also reports membership of the NIHR HTA Programme General Funding Committee. IC reports NIHR Health Technology Assessment Programme commissioned research grant institutional funding to deliver the trial (Ref 13/140/05). He also reports grants or contracts from Janssen-Cilag and Eli Lilly. He reports personal consultancy fees from Eli Lilly & Company (USA), Astra-Zeneca plc, MSD, Merck Serono, Bristol Meyers Squibb Inc (USA), Bayer Pharmaceuticals, Roche AG (Switzerland), OncXerna (China), Boehringer Ingelheim (Germany), Incyte Inc (USA), Astellas Pharma (Japan), GlaxoSmithKline Ltd (UK), SOTIO (Czech Republic), Eisai (Japan), Daiichi-Sankyo, Taiho, Servier Laboratories, Seagen, Turning Point Therapeutics and Novartis. He also reports honoraria from Eli Lilly, Eisai, Servier, and Roche and participation on a Data

Safety Monitoring Board or Advisory Board for Five Prime Therapeutics, Bristol Myers Squibb Inc., and Symphogen. MC reports NIHR Health Technology Assessment Programme commissioned research grant institutional funding to deliver the trial (Ref 13/140/05). He also reports membership of the NIHR CRSU Funding Board, NIHR HTA Funding Committee, NIHR HTA Prioritisation Committee B Methods Group, and NIHR HTA General Committee. DFM reports NIHR Health Technology Assessment Programme commissioned research grant institutional funding to deliver the trial (Ref 13/140/05). He also reports unrelated research grants from NIHR, Innovate UK, Medical Research Council (MRC), Novavax Inc (U.S.), the Northern Ireland HSC R&D Division, Randox Laboratories, and the Wellcome Trust as well as personal fees from Bayer, Aptarion, Direct Biologics, Aviceda, GlaxoSmithKline Ltd (UK), Boehringer Ingelheim (Germany), Novartis, Eli Lilly & Company (USA) and SOBI. He reports participation in Data Safety Monitoring Boards for Vir Biotechnology, Inc and Faron Pharmaceuticals. He holds a patent for novel treatment for inflammatory disease with Queen's University Belfast. He also reports spousal personal fees from Insmid and the California Institute for Regenerative Medicine. He is co-director of research for the Intensive Care Society (UK), Programme Director of the NIHR/MRC Efficacy & Mechanisms Evaluation (EME) Programme, and Scientific Director for NIHR Programmes. RM reports NIHR Health Technology Assessment Programme commissioned research grant institutional funding to deliver the trial (Ref 13/140/05). He also reports research grants from the NIHR HTA Programme, NIHR EME Programme, Wellcome Trust, Medical Research Council, NI Chest, Heart & StrokeHeart & Stroke Association, and Randox Laboratories Ltd (UK), all unrelated to the submitted work. He was also a member of the NIHR HTA Programme Prioritisation Committee B and the NIHR EME Programme funding committee. RP reports NIHR Health Technology Assessment Programme commissioned research grant institutional funding to deliver the trial (Ref 13/140/05) and membership of the NIHR EME Funding Committee. CF, RAB, AD, CM, DS, ALT, and RHW report NIHR Health Technology Assessment Programme commissioned research grant institutional funding to deliver the trial (Ref 13/140/05) but no other competing interests. MG reports no competing interests.

Financial report

This study was funded by the UK NIHR HTA programme (HTA Project: 13/140/05). The views expressed are those of the authors and not necessarily those of the (NIHR) or the UK Department of Health and Social Care.

Trial registration

ISRCTN: 84288963. Registered 1 July 2015.
EudraCT: 2015-002830-35.

Data presented previously

Preliminary analyses were presented at the European Confederation of Clinical Microbiology and Infectious Diseases (ECCMID) and the European Society for Medical Oncology (ESMO) congress in 2021 but the results have not been published elsewhere.

Data availability

Requests for access to de-identified patient data can be made by researchers to the chief investigators, and data will be shared subject to any constraints. Requests for access should be accompanied by a proposal describing the aims and scope of the research, details of the data requested, and data analysis plan. Proposals will

be considered by the Trial Management Group, co-investigators, and Sponsor who will make a decision regarding data access. A data-sharing agreement will be signed between the researchers, principal investigators, and Sponsor.

Acknowledgements

The trial team are grateful for the invaluable contribution that patients and their carers have made to this research and wish to acknowledge those who considered participation in the trial as well as patients who enrolled as participants. We acknowledge the contribution towards trial management made by members of staff at the Northern Ireland Clinical Trials Unit. The trial team are grateful to staff at Belfast Health & Social Care Trust for supporting the conduct of the trial; specifically, the Research Office staff for undertaking trial sponsorship and Mrs Margaret McFarland for pharmacovigilance support. In addition to the investigators at study sites, the trial was made possible by the work of several other members of clinical and support staff at each site that was opened for participant recruitment. We thank the trial oversight committees, particularly the independent members and patient representatives of each committee, for the guidance and support provided. The independent Data Monitoring Committee comprised Dr Mark Saunders (chair), Dr Ashley Jones, and Prof Paul Dark. Independent members of the Trial Steering Committee were Prof Kathy Bamford (chair), Prof Christian Ottensmeier, Mr Richard Jackson, Capt Robert Gray, and Dr Ed Goodall.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cmi.2023.07.021>.

References

- [1] Schimpff S, Satterlee W, Young VM, Serpick A. Empiric therapy with carbenicillin and gentamicin for febrile patients with cancer and granulocytopenia. *N Engl J Med* 1971;284:1061–5. <https://doi.org/10.1056/NEJM197105132841904>.
- [2] The National Institute for Health and Care Excellence. Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients. NICE; 2012. <https://www.nice.org.uk/guidance/cg151/evidence/full-guideline-188303581>. [Accessed 19 January 2019].
- [3] National Chemotherapy Advisory Group. Chemotherapy services in England: ensuring quality and safety a report from the national chemotherapy advisory group. NCAG; 2009. <http://ncat.nhs.uk/sites/default/files/NCAG%20Report.pdf>. [Accessed 19 January 2019].
- [4] Klasterksy J, de Naurois J, Rolston K, Rapoport B, Maschmeyer G, Aapro M, et al. Management of febrile neutropenia: ESMO clinical practice guidelines. *Ann Oncol* 2016;27:v111–8. <https://doi.org/10.1093/annonc/mdw325>.
- [5] Taplitz RA, Kennedy EB, Bow EJ, Crews J, Gleason C, Hawley DK, et al. Outpatient management of febrile and neutropenia in adults treated for malignancy: American society of clinical oncology and infectious diseases society of America clinical practice guideline update. *J Clin Oncol* 2018;36:1443–53. <https://doi.org/10.1200/JCO.2017.77.6211>.
- [6] Simmons T. An assessment of need. NS: prevention and management of neutropenic sepsis in cancer patients. 2012. <https://www.nice.org.uk/guidance/cg151/evidence/needs-assessment-pdf-188303583>. [Accessed 19 January 2019].
- [7] Rubenstein EB, Rolston K, Escalante C, Manzullo E, Hughes P, Fender A, et al. Outpatient management of febrile episodes in low risk neutropenic patients with cancer. *Cancer* 1993;71:3640–6. [https://doi.org/10.1002/1097-0142\(19930601\)71:11<3640::AID-CNCR2820711128>3.0.CO;2-H](https://doi.org/10.1002/1097-0142(19930601)71:11<3640::AID-CNCR2820711128>3.0.CO;2-H).
- [8] Forde C, McMullan R, Clarke M, Wilson RH, Plummer R, Grayson M, et al. Early switch from intravenous to oral antibiotic therapy in patients with cancer who have low-risk neutropenic sepsis (the EASI-SWITCH trial): study protocol for a randomised controlled trial. *Trials* 2020;21:431. <https://doi.org/10.1186/s13063-020-04241-1>.
- [9] Piaggio G, Elbourne DR, Pocock SJ, Evans SJW, Altman DG, CONSORT Group. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *JAMA* 2012;308:2594–604. <https://doi.org/10.1001/jama.2012.87802>.
- [10] International conference on harmonisation of technical requirements for registration of Pharmaceuticals for human use. ICH harmonised tripartite guideline: statistical principles for clinical trials E9. London, England: European Medicines Agency; 1998.
- [11] Non-inferiority clinical trials to establish effectiveness. Guidance for industry. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/non-inferiority-clinical-trials>. [Accessed 19 January 2019].
- [12] Vidal L, Ben Dor I, Paul M, Eliakim-Raz N, Pokroy E, Soares-Weiser K, et al. Oral versus intravenous antibiotic treatment for febrile neutropenia in cancer patients. *Cochrane Database Syst Rev* 2013;2013:CD003992. <https://doi.org/10.1002/14651858.CD003992.pub3>.
- [13] Kern WV, Cometta A, De Bock R, Langenaeken J, Paesmans M, Gaya H. Oral versus intravenous empirical antimicrobial therapy for fever in patients with granulocytopenia who are receiving cancer chemotherapy. International antimicrobial therapy cooperative group of the European Organization for Research and Treatment of Cancer. *N Engl J Med* 1999;341:312–8. <https://doi.org/10.1056/NEJM199907293410502>.
- [14] Giamarellou H, Bassaris HP, Petrikos G, Busch W, Voulgarelis M, Antoniadou A, et al. Monotherapy with intravenous followed by oral high-dose ciprofloxacin versus combination therapy with ceftazidime plus amikacin as initial empiric therapy for granulocytopenic patients with fever. *Antimicrob Agents Chemother* 2000;44:3264–71. <https://doi.org/10.1128/AAC.44.12.3264-3271.2000>.