Contemporary use of antimicrobial prophylaxis for surgical patients: a mixed methods study

Statistical Analysis Plan

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1. Introduction

Background and rationale

Surgical site infections (SSIs) are a common post-operative complication affecting an estimated 250,000 NHS patients each year. [1-3] Patients who develop these infections are adversely affected with delayed recovery, prolonged hospitalisation and increased mortality. Moreover the treatment of SSIs are expensive and represent a significant burden on healthcare resources. [1 4] Antimicrobial drugs are commonly used around the time of surgery with the aim of preventing surgical site infections. These drugs are only one component of a multimodal strategy to prevent SSIs including pre-operative showers and hand washing techniques. Despite this, anecdotal evidence suggests an over-reliance on antimicrobial drugs, with many doctors giving more doses than recommended. The resultant overuse is a major contributor to antimicrobial resistance, which has recently been identified as an emerging global public health crisis.

National guidelines (NICE & SIGN) provide detailed recommendations [5 6] based on the likely infecting organisms for a given procedure, patient risk factors, procedure risk factors and drug allergies. However, we suspect that there is substantial heterogeneity of clinical practice. This may in part be due to the low quality of evidence presently available to inform clinical decision making, and in part due to differential interpretation of the primary evidence and the clinical guidelines. Our aim was to conduct a prospective clinical audit to describe current clinical practice across NHS hospitals.

We conducted a prospective multi-centre observational cohort study to measure compliance with local and national guidelines relating to antimicrobial prophylaxis for surgery. At the same time, we carried out a national survey of clinicians to investigate decision-making and behaviours regarding the provision of antimicrobial prophylaxis for surgical patients.

Objectives

- To investigate the adherence to national and local guidelines surrounding antimicrobial prophylaxis prescribing across selected high volume surgical procedures.
- To measure the incidence of infections and antimicrobial-related complications in patients undergoing surgery.
- To understand the attitudes, decision making and potential concerns on antimicrobial prophylaxis from clinicians.

2. Methods

A mixed-methods approach including an observational cohort study and survey of clinical practice.

Study design and setting

The multicentre observational cohort study was conducted as a service evaluation at 12 NHS hospitals. Data was collected prospectively over a 30-day period of patients undergoing a pre-defined list of surgical procedures listed in the section below. Only routinely collected data was used to answer our objectives. There was no additional patient or primary care contact.

Participants and data collection

Patients were aged 18 years and over at participating centres undergoing one of the following surgical procedures:

- Colorectal resection
- Elective Caesarean section
- Abdominal hysterectomy
- Vaginal hysterectomy
- Primary hip replacement
- Primary knee replacement
- Transurethral resection of prostate
- Transurethral resection of bladder tumour
- Open surgery for closed long bone fracture (leg or arm)

Open, robotic, laparoscopic, laparoscopically assisted and laparoscopic procedures converted to open are all eligible versions of the above procedures.

Data was collected on paper case report forms (CRF) and uploaded to the online electronic CRF (e-CRF) via a secure data web entry portal. A thorough data cleaning procedure will be implemented as follows:

- Validation checks within the eCRF; The e-CRF provides a warning message and asks the user to confirm the value of any data entered which lie outside the pre-determined validity range (hard and soft ranges), e.g. if haemoglobin is less than 30 g/L or age greater than 100 years.
- Data checking for duplicates
- Handling of missing data as outlined in section 4

3. Exposures and outcomes

Exposures

Adherence to guidelines on the administration of antimicrobial prophylaxis for surgery

Primary outcome

Surgical site infection (superficial, deep, body cavity)

Secondary outcomes

- Antimicrobial related complications
- Number of doses for prophylaxis
- Number of doses for treatment of infection
- Number of infections
- Mortality

4. Statistical analysis

Characteristics of the cohort

The following characteristics will be presented overall.

- Age, mean (SD) and median (IQR)
- Gender, n (%)
- ASA grade (I, II, III, IV), n (%)
- Documented drug allergies – n (%)
- Risk factors (obesity, antibiotics for pre-existing infection, immunosuppressant disease, active malignancy, current smoker, Diabetes mellitus, poor nutritional state,

immunosuppressant drugs, know carrier of resistant organism, chemo or radiotherapy), n (%)

- Anaesthetic technique (general, spinal, epidural, other regional), n (%)
- Surgical procedure (colorectal resection, elective Caesarean section, abdominal hysterectomy, vaginal hysterectomy, primary hip replacement, primary knee replacement, transurethral resection of prostate, transurethral resection of bladder tumour, open surgery for closed long bone fracture), n (%)
- Wound contamination, n (%)
- Duration of surgery (<2, 2-<4, 4-<6, >6 hours), n (%)

Analysis

Descriptive analysis

We will report the total number (%) of patients that received antimicrobial drugs, stratified by whether the prescription was consistent with guidelines on antimicrobial prophylaxis for surgery. We will present these data by surgical procedure category.

Other data summaries that will be reported will include the following:

- Adherence to guidelines
- Antimicrobial use during and after surgery
- Infection after surgery by ISOS and Clavien-Dindo grading systems
- Antimicrobial complications associated with antimicrobial use
- Re-intervention and hospital stay within 30 days of surgery

Inferential analysis

Binary outcomes:

1. Surgical site infection

Count outcomes:

1. Total number of doses for prophylaxis
2. Total number of infections
3. Total number of doses for treatment of infection

To investigate the baseline risk factors and associations with the outcome and the main exposure of interest (adherence to guidelines) we will perform a mixed effects negative binomial regression or a mixed effects logistic regression model with a random intercept for site, adjusted by all other recorded variables one at a time. These effect estimates will be compared with the crude effect estimates for the main exposure. Using the “10-percent-rule”

the “change-in-estimate” (CIE) approach will be used to decide whether to include potential confounders in the causal model. Finally, a mixed effects negative binomial model will be fitted to estimate the effect of the exposure of interest on the outcome, adjusted for any confounders.

We will also assess the association between the total number of doses for prophylaxis and SSI using the above approach.

The baseline risk factors we will consider are as follows: age, gender, surgical procedure, current smoker, pre-existing antimicrobial use, diabetes mellitus, ASA, wound contamination, duration of surgery, immunosuppressant disease, immunosuppressant drugs, chemo or radiotherapy, carrier of a resistant organism, poor nutritional state and obesity.

Sensitivity analysis

The categorisation of whether guidelines on antimicrobial prophylaxis were followed is based on self-assessment by the clinical team involved. We will report the proportion of patients who received prophylaxis according to guidelines, stratified by whether the first dose of antimicrobials was given before the induction of anaesthesia and within 60 minutes of the surgical incision. We will re-categorise the exposure according to these three criteria and repeat the primary analysis.

Handling of missing data

Patients missing outcome measure data will be excluded from the analysis.

Exclusions

Patients who undergo hepatobiliary surgery will be dropped from all analyses.

5. Clinician survey

We conducted an online survey for clinicians involved in the provision or administration of antimicrobial prophylaxis for surgery, including: surgeons, anaesthetists and microbiologists. The survey was comprised of multiple-choice questions, rating scales and free text to compare clinician viewpoints and perceived barriers surrounding antimicrobial prophylaxis with actual practice. The key themes explored in the questionnaire were:

(1) Factors affecting clinicians’ decisions on antimicrobial prophylaxis that would result in deviations from the local guidelines. This could include patient risk factors, type of procedure.

(2) Attitudes towards the harms associated with antimicrobial prophylaxis and how this would influence the quantity of antimicrobials a patient receives.

(3) Clinician's willingness to participate in a clinical trial that will randomise patients to receive different quantities of antimicrobials (including the possibility of some receiving no drugs at all for surgery). This is to help develop an intervention that could reduce antimicrobial use without compromising patient safety and ultimately change clinical practice.

The survey was distributed via an online survey tool to surgeons, anaesthetists and microbiologists. The survey data will be analysed and reported using descriptive statistics (frequency (%) for categorical data or median (range) for continuous data). Answers to the free text questions will be analysed using deductive and inductive content analysis (Ref). Data will be initially managed in Microsoft Excel and coded manually. Two members of the study team will generate codes and categories emerging from the data inductively. This will be done independently.

6. References

1. International Surgical Outcomes Study g. Global patient outcomes after elective surgery: prospective cohort study in 27 low-, middle- and high-income countries. *Br J Anaesth* 2016;117(5):601-09.
2. Abbott TEF, Fowler AJ, Dobbs TD, et al. Frequency of surgical treatment and related hospital procedures in the UK: a national ecological study using hospital episode statistics. *Br J Anaesth* 2017;119(2):249-57.
3. Fowler AJ, Abbott TEF, Prowle J, et al. Age of patients undergoing surgery. *Br J Surg* 2019;106(8):1012-18.
4. GlobalSurg C. Surgical site infection after gastrointestinal surgery in high-income, middle-income, and low-income countries: a prospective, international, multicentre cohort study. *Lancet Infect Dis* 2018;18(5):516-25.
5. A summary of selected new evidence relevant to NICE clinical guideline 74 “Prevention and treatment of surgical site infection” (2008). Evidence update 43 2013. National Institute for Health and Care Excellence. (http://www.nice.org.uk/guidance/cg74/evidence).
6. Antibiotic prophylaxis in surgery. July 2008, updated April 2014. Scottish Intercollegiate Guidelines Network. Edinburgh: Healthcare Improvement Scotland; (http://www.sign.ac.uk/assets/sign104.pdf).

7. Appendix 1: Dummy tables

Table 1: Patient baseline and operative characteristics

Patient baseline and operative characteristics	Number of patients with available data – no. (%)	Summary measure
Gender – no. (%)		
Male		
Female		
Age (years)		
Mean (SD)		
Median (IQR)		
[a] American Society of Anaesthesiology grade – no. (%)		
I		
II		
III		
IV		
Documented drug allergies – no. (%)		
Yes		
No		
[b] Risk factors – no. (%)		
Obesity (BMI ≥ 30)		
Antibiotics for pre-existing infection		
Immunosuppressant disease		
Active malignancy		
Current smoker		
Diabetes mellitus		
Poor nutritional state (e.g. BMI <20)		
Immunosuppressant drugs		
Known carrier of resistant organism e.g. MRSA		
Chemo or Radiotherapy (within last 3 months)		
Anaesthetic technique – no. (%)		
General		
Spinal		
Epidural		
Other regional		
Surgical procedure category – no. (%)		
Colorectal resection		
Elective Caesarean section		
Abdominal hysterectomy		
Vaginal hysterectomy		
Primary hip replacement		
Primary knee replacment		
Transurethral resection of prostate		
Transurethral resection of bladder tumour		
Open surgery for closed long bone fracture (leg or arm)		
Wound contamination during surgery – no. (%)		
Yes		

No		
Operative time – no. (%)		
0-<2 hours		
2-<4 hours		
4-<6 hours		
> 6 hours		

Abbreviations: SD, standard deviation; IQR, Interquartile range

[a] American Society of Anaesthesiology grades are defined as follows (grade 5 patients were not eligible for inclusion): 1, a healthy patient; 2, a patient with mild systemic disease that does not limit physical activity; 3, a patient with severe systemic disease that limits physical activity; and 4, a patient with severe systemic disease that is a constant threat to life.

b Patient may have more than one risk factor.

Table 2: Adherence to guidelines

Guidelines – no. (%)	Number of patients with available data – no (%)	Summary measure		
		Yes	No	Don't know
Local guidelines				
First dose of antimicrobials administered before induction of anaesthesia				
First dose of antimicrobials within 60 minutes before surgical incision				

Table 3: Antimicrobial administration during and after surgery

Antimicrobial administration	Number of patients with available data – no. (%)	Summary measure
Prophylactic antimicrobial use		
Start of surgery – no. (%)		
Number of doses		
Mean (SD)		
Median (IQR)		
Further antibiotics during surgery – no. (%)		
Number of doses		
Mean (SD)		
Median (IQR)		
After surgery – no. (%)		
Number of doses		
Mean (SD)		
Median (IQR)		
Therapeutic antimicrobial use to treat an infection - no. (%)		
Indication - no. (%)		
Route of antimicrobial administration - no. (%)		
Intra-venous		
Oral		
Patient discharged with an antimicrobial prescription - no. (%)		
Total duration of all therapeutic antimicrobials (days)		
Mean (SD)		
Median (IQR)		
Total number of antimicrobial doses administered		
Mean (SD)		
Median (IQR)		
Antibiotic class - no. (%)		
None		
Cefuroxime		
Co-Amoxiclav		
Metronidazole		
Gentamicin		
Teicoplanin		
Other		

Table 4: Adherence to guidelines by surgical procedure

Number of patients that received antimicrobial drugs consistent with guidelines – no (%)	Summary measure		
	Yes	No	Don't know
Surgical procedure category – no. (%)			
Colorectal resection			
Elective caesarean section			
Abdominal hysterectomy			
Vaginal hysterectomy			
Primary hip replacement			
Transurethral resection of prostate			
Transurethral resection of bladder tumour			
Open surgery for closed long bone fracture (leg or arm)			

Table 5: Outcomes after surgery

Infections – no. (%)	Number of patients with available data – no. (%)		Summary measure					
	ISOS	Clavien-Dindo	ISOS Grade				Clavien-Dindo Grade	
			None	Mild	Moderate	Severe	I-II	III-V
Superficial surgical site								
Deep surgical site								
Body cavity								
Pneumonia								
Urinary tract								
Bloodstream								
Other								

Table 6: Reintervention and hospital stay within 30 days of surgery

Reintervention and hospital stay within 30 days of surgery	Number of patients with available data – no. (%)	Summary measure
Surgery to treat surgical site infection – no. (%)		
Re-admission to critical care – no. (%)		
Endoscopy or interventional radiology procedure – no. (%)		
Status at hospital discharge – no. (%)		
Alive		
Dead		
Length of stay (days)		
Mean (SD)		
Median (IQR)		

Table 7: Harms associated with antimicrobial use

Potential antimicrobial side effects	Number of patients with available data – no. (%)	Summary measure		
Antimicrobial related harms – no. (%)		**Yes**	**No**	**Suspected**
Anaphylaxis				
Acute kidney injury				
Angioedema				
Diarrhoeal illness				
Patient reported hearing loss				
Other				
Rash or pruritus				
Acute kidney injury				
Other				

Figure 1: Patient flow chart