Protocol

CO-GENT: Clinical Outcomes in Gentamicin Prescribing and Monitoring in United Kingdom Hospitals

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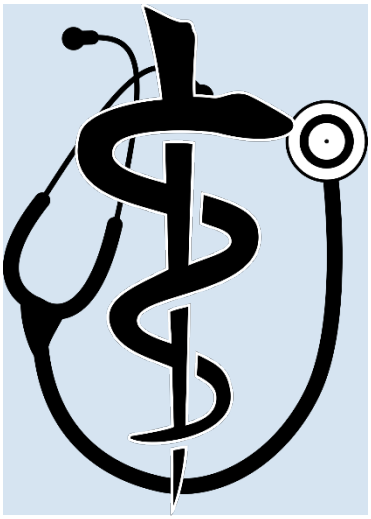
Gentamicin
National Audit



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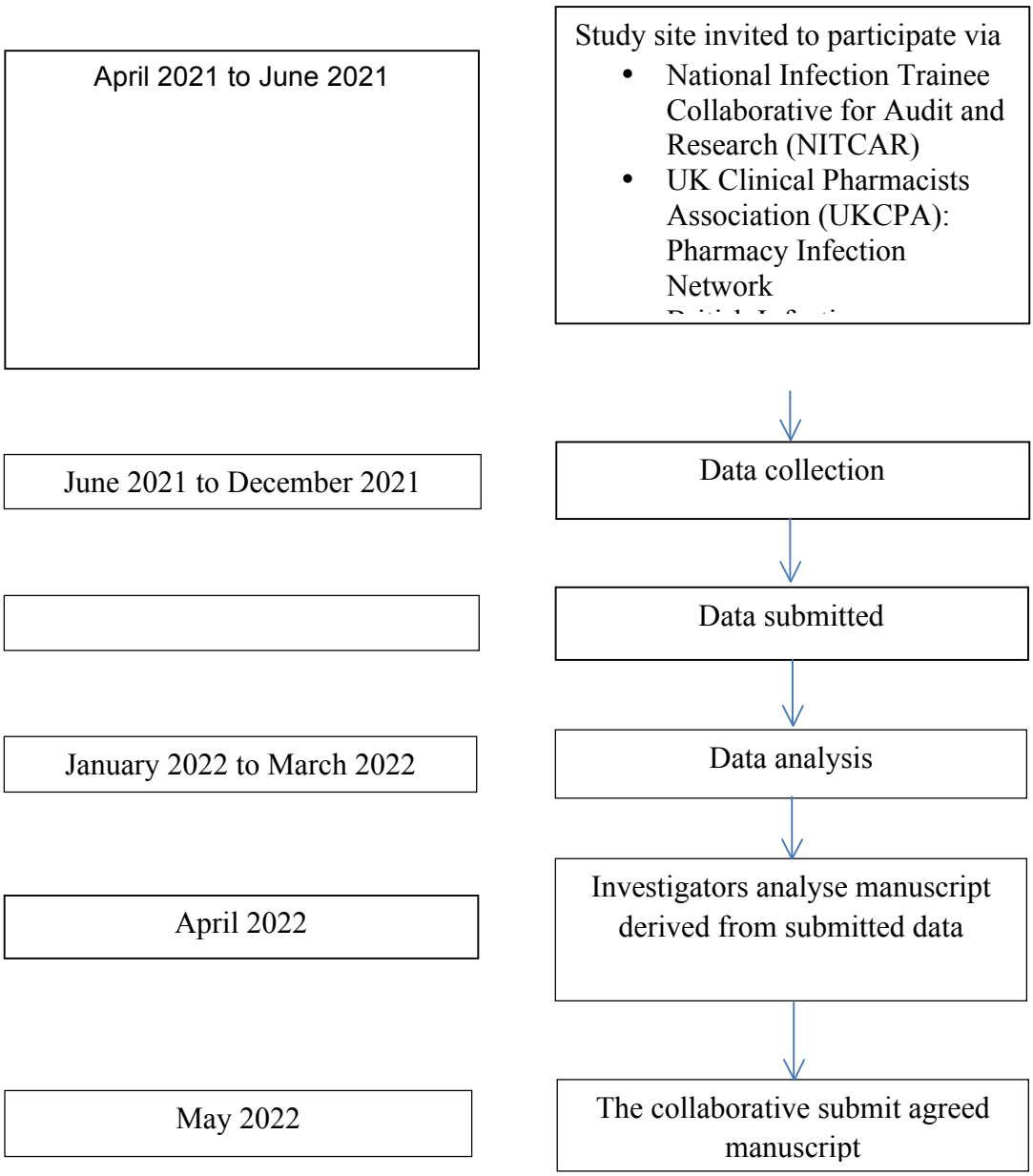
PROTOCOL SUMMARY

Title:	CO-GENT: Clinical Outcomes in Gentamicin Prescribing and Monitoring in United Kingdom Hospitals
Précis:	A multicentre audit and service evaluation of extended-interval gentamicin prescribing and monitoring (GPM), to assess current practice, audit practice against local policies and describe clinical outcomes using different strategies in GPM. Data can be collected from June 2021 to December 2021.
Objectives:	Primary: to compare common dosing and monitoring strategies for gentamicin, using clearly defined clinical outcomes, as well as audit of each participating Trust according to its own local gentamicin policy Secondary: to determine which prescribing and monitoring aid(s), including EPMA (electronic prescribing and medicine administration) and dosing calculators, improve clinical outcomes and adherence to local policy
Population:	Patients will be included according to the following criteria: Adult patients (> 18 years) given at least one dose of gentamicin and having at least one gentamicin level, during the data collection period. Patients will be excluded for any of the following: endocarditis; conditions that significantly alter the volume of distribution of gentamicin (burns, cystic fibrosis, ascites, pregnancy); renal replacement therapy; current inpatients in intensive care; other exclusion criteria as per local GPM policies.
Number of Sites:	A minimum of 75 UK centres, up to a maximum of 100.
Study Duration:	12 months (6 months recruitment and data collection, 3 months follow up, 3 months data editing and analysis)
Study investigators	Gentamicin prescribing and monitoring (GPM) is managed primarily by ward doctors, antimicrobial pharmacists, and infection doctors. The data collected reflects this shared management. The involvement of a named staff member from all specialties will help all data fields be completed. A

statistician will be vital for study design and analysis.

Schematic of Study Dates:



1.1 Background Information

Gentamicin is an aminoglycoside antibiotic with a wide spectrum of activity against Gram negative bacteria (as well as some Gram positive cocci) and a rapid, dose-dependent bactericidal effect. However, aminoglycosides have a narrow therapeutic index, with significant risks of nephrotoxicity and irreversible ototoxicity, which increase with the duration of therapy. Gentamicin therefore requires careful dosing and close monitoring of levels to achieve therapeutic concentrations, whilst minimising the risk of toxicity (Electronic Medicines Compendium 2018).

Historically, multiple daily dosing (also known as 'conventional' dosing) strategies were employed during gentamicin therapy. These regimens used total daily doses of 3-5mg/kg, divided into three doses (Nicolau 1995). The discovery of a prolonged 'post-antibiotic effect' (Stubbings 2006) of gentamicin led to the development of reduced frequency regimens, with potentially lower risk of adverse effects. In the 1990s, 'extended' daily dosing regimens largely replaced conventional dosing, with studies showing comparable effectiveness and reduced renal toxicity (Nicolau 1995, Urban).

Extended daily dosing was shown to be superior to conventional dosing. A number of different protocols for extended daily dosing and monitoring arose simultaneously at different centres. Several of these were adopted more widely than others, particularly the Hartford, Barnes-Jewish and Urban-Craig nomograms, as well as the popular system of pre-dose monitoring without a nomogram. However, there are very few studies directly comparing these approaches (Lee 2014), and there is no consensus on which one(s) are the most effective, safe and easy to follow. This is particularly relevant given recent EUCAST guidance suggesting that gentamicin may be under-dosed in relation to traditional breakpoints for most organisms for which gentamicin is used (European Committee on Antimicrobial Susceptibility Testing 2020).

A recent regional audit of gentamicin prescribing and monitoring (GPM) in the northwest of England (161 patients, data collected from November 2019 to January 2020) revealed a wide variety of practice across NHS Trusts, with correct dosing and monitoring according to Trusts' own local policies being well below the audit standard of 95% (correct first and second doses 62% and 69% respectively; correct timing of first and second levels 63% and 69% respectively). There was a higher rate of acute kidney injury in Trusts using nomograms (15%, with 95% CI 6 to 24%) compared with pre-dose levels (8%, with 95% CI 2 to 14 %), however the difference was not significant (Huq 2020, unpublished).

There is no clinical guideline for GPM that is widely used in the UK. Local variation in practice may contribute to suboptimal GPM; compounded by regular rotation of junior doctors, nurses and pharmacists between different organisations. There are recommendations in pharmacy guidelines (UKMi 2018) as well as the BNF, however these reflect expert opinion and supportive clinical evidence is lacking.

It has previously been shown that a single dose of gentamicin (without further doses) is safe even at reduced renal function at the time of administration (Cobussen 2020), and would not require monitoring of levels. Since a major objective of our study is to determine the optimal approach to monitoring, we will exclude patients who have only received a single dose of gentamicin, without having a follow-up gentamicin level.

A working group in the northwest is currently in the process of developing a regional guideline for gentamicin. The leadership of this group intend to help develop a national guideline in due course. A national audit dataset would be used to inform best practice for developing a national gentamicin guideline.

1.2 Rationale

The optimal strategy for GPM is uncertain owing to lack of clinical evidence. In order to obtain such evidence, clinical epidemiological data are required to define the state of GPM in the United Kingdom NHS setting. These data will inform the design of a study into GPM e.g. outcome rates to inform sample size calculations. To obtain such data an audit of practice related to GPM will be carried out, in combination with a service evaluation.

1.3 Study Objectives

1- To describe the demographic and clinical characteristics of patients given gentamicin

2- To obtain outcome rates (see 1.4 Outcome Measures) in patients given gentamicin

3- To assess compliance with the audit standards previously derived from pilot study data (for details on the standards, see Audit Data Collection Tool, ‘Tab B’)

4- To associate dosing and monitoring strategies with outcomes

5- To describe practice variation in gentamicin prescribing and monitoring (GPM), using a combination of quantitative and qualitative data

1.4 Study Outcome Measures

Primary outcomes:

1. Rate of acute kidney injury in patients given at least one dose of gentamicin (using an extended daily dosing regimen) AND who had at least one gentamicin level taken

2. Compliance with audit standards (see Audit Data Collection Tool, 'Tab B')

Secondary outcomes:

3. All-cause mortality at 30 days from first dose of gentamicin

4. Number of days hospitalisation within 30 days of first dose of gentamicin

5. Total duration of antibiotic treatment (see supplementary guide to Audit Data Collection Tool for definition of total duration)

6. Collection of categorical data to characterise GPM at each participating Trust, by review of local gentamicin policy and qualitative feedback from reporters (See Audit Data Collection Tool, 'Tab D')

AKI will be defined using KDIGO criteria (appendix 1). Data on potential confounders of AKI will be collected, including nephrotoxic medications, diagnosis of diabetes, uncontrolled hypertension, red-flag sepsis and urinary tract obstruction.

For each of the above primary and secondary outcomes, between group comparisons will be made for the following: centres using nomograms for monitoring versus those using pre-dose levels; centres using dosing calculators versus those with alternative dosing tools; centres using EPMA versus those without EPMA; 5mg/kg initial doses versus alternative initial doses; total number of doses of gentamicin given during therapy.

1.5 Study design

Design: Observational multicentre cohort study. Data can be collected retrospectively within the previous 60 days. Each participating centre will be asked to submit 20 patients.

The study population is hospitalised adults within NHS Trusts, given at least one dose of gentamicin (using an extended dosing protocol), and having at least one gentamicin level. The inclusion of a minimum of one gentamicin level being taken, ensures that recruited patients are those being considered for more than one single dose of gentamicin. This allows evaluation of gentamicin monitoring strategies, as well as dosing, which are the main objectives of the study.

Data can be collected by any infection specialty doctor (registrars or Consultants in Microbiology or Infectious Diseases, or more junior trainee or student with interest in the specialism) or antimicrobial pharmacist, or trainee pharmacists with an interest in antimicrobials.

Timeline

- Start of data collection: June 2021
- End of data collection: December 2021
- Data collection methods: identify eligible patients from list of gentamicin levels from the previous 30 days, obtained from the local biochemistry or microbiology department
- Duration of follow up: 30 days from initial dose of gentamicin

1.6 Subject Inclusion Criteria

Patients may be included according to the following criteria: adult patients (> 18 years) with at least one dose of gentamicin (using an extended dosing protocol) AND at least one gentamicin level. For the protocol on patient selection, see section 1.8.

1.7 Subject Exclusion Criteria

Patients are excluded if they have any of the following:

1. Contraindications to gentamicin: myasthenia gravis or known hypersensitivity.

2. If there is no evidence of active infection: surgical prophylaxis, routine change of long-term urinary catheters

3. Conditions where the volume of distribution of gentamicin may be significantly altered (this makes extended interval dosing unsuitable): ascites, burns (>20% body surface area), cystic fibrosis, patients admitted to intensive care

4. Patients on renal replacement therapy (RRT) prior to admission; this does not include patients who required RRT due to AKI 3 during their hospital admission

5. Infective endocarditis

Conditions for inclusion and exclusion are summarised in Table 1. These lists are for guidance and are not exhaustive; clarification can be sought on other conditions not listed.

Table 1: Clarification of which patients are to be included and excluded

Included conditions	**Excluded conditions**
Given at least one dose of gentamicin using an extended dosing protocol AND has had at least one gentamicin level	Myasthenia gravis
Adult patients only (>18)	Known hypersensitivity to gentamicin
	Surgical prophylaxis
	Routine change of long-term urinary catheters
	Endocarditis
	Burns (>20% total body surface area)
	Ascites
	Cystic fibrosis
	Renal replacement therapy
	Current inpatient in intensive care , prior to giving the first dose of gentamicin
	Paediatric patients

1.8 Strategies for Recruitment and Retention

Patients will not be formally recruited.

Information governance approval will be requested at each site to complete this study as an audit and service evaluation. Information governance approval will be applied for at the lead Trust – Lancashire Teaching Hospitals NHS Foundation Trust.

Each participating centre will submit 20 patients to the study. To minimise selection bias and ensure that screened patients are those being considered for more than a single dose of gentamicin, our recommend screening process is as follows:

- to contact the local biochemistry lab for a list of gentamicin levels from the previous 60 days
- from the list of gentamicin levels, select 20 different patients at random

1.9 Study Procedures/Evaluations/ Questionnaire

Data will be collected on MS Excel spreadsheets to facilitate ease of investigator collection and submission. For information governance, patient identifier data will be stored locally, but will not be sent on to the national audit team. Data cleanup and editing will be performed by the lead investigator on MS Excel.

1.10 Sample Size Considerations

Each investigator will be required to submit a minimum 20 patients' data to the national data set. We estimate this taking approximately 8 hours for one investigator to complete the audit locally. The time commitment per person can be reduced by sharing the workload amongst several local investigators, with a single designated lead to act as a point of contact. The regional audit collected data on 161 patients, across 15 hospital Trusts. In the national audit, a total sample size of at least 1500 will be sought: this would require complete datasets from at least 75 centres. This number is based on a power calculation derived from the northwest regional pilot data, which suggested that detection of a 5% difference in AKI rate between Trusts using nomograms and those with pre-dose monitoring, with 80% statistical power and 95% confidence intervals, requires 1408 patients.

1.11 Final Analysis Plan

Data will be requested within one month of the end of the data collection period, with a follow up time of two months after the end of the data collection period. Data analysis will be completed over the subsequent three months. Results are reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for observational studies (von Elm 2007). Data will be analysed with reference to compliance with audit standards. Data will be analysed as proportions. Statistical analyses using a generalised linear model (also called multivariable regression analysis) will be performed on the statistical software package 'R' with the aid of a statistician. The full detail of the statistical analysis plan is yet to be completed.

1.12 Publication/data sharing policy

All investigators submitting data on 20 patients will be eligible to be listed as authors on the manuscript written by the principal investigators (Huq, Reddy, Clark) and therefore contribute academically, as long as they remain contactable and fulfil the remainder of the ICMJE criteria for authorship (which they will be given an opportunity to fulfil). Contributions other than by submission of data on 20 patients may lead to inclusion as an author on the manuscript, at the discretion of the project leads. The ordering of authors will be at the discretion of the project leads. See the NITCAR "Policy on authorship of projects supported by NITCAR, version 1.0", which is adopted by this project in full, for further details.

1.13 References

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Appendix 1

AKI will be defined using KDIGO (2012) criteria, with staging as follows:

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR ⩾0.3 mg/dl (⩾26.5 µmol/l) increase	<0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ⩾12 hours
3	3.0 times baseline OR Increase in serum creatinine to ⩾4.0 mg/dl (⩾353.6 µmol/l) OR Initiation of renal replacement therapy OR, In patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m^2	<0.3 ml/kg/h for ⩾24 hours OR Anuria for ⩾12 hours