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SURGERY | RESEARCH ARTICLE

Non-compliance in gentamicin prescribing and administration: A patient safety issue

Ellen Murgitroyd^{1,2*}, Sarah Farquharson³ and Niall Poole¹

Abstract: *Importance:* Extensive use of antibiotics requiring dose-monitoring and weight-based prescribing can reduce compliance, risking morbidity, and mortality from sepsis. *Objective:* To determine if gentamicin was being prescribed according to recommendations in the British National Formulary and trust guidelines. *Methods:* All patients prescribed gentamicin in a one-month period on electronic prescribing were included. Data comprised demographics, admission specialty, dosing regime prescribed, number of doses received, actual dose, and recorded reasons for non-administration. *Results:* 374 patients were prescribed gentamicin over one month. 223 were prescribed stat doses (207 received, 16 not given; 93% compliance). The remaining 151 patients were on multidose prescriptions, between 3 and 7 doses. 25 received zero doses, 41 a single dose, 50 patients received two doses, and 35 received three doses or greater (23% compliance with guidelines). *Conclusion:* Antibiotics are essential in treating and preventing sepsis but must be used appropriately. Sensitivities should be used to guide antibiotic prescription; however, generic guidelines must consider the practicalities of antibiotic regimes requiring weight-based dosing and monitoring. When it is necessary, these regimes can be easily adhered to, but when the guidelines result in large numbers of patients requiring monitoring, compliance will be affected, and as a result morbidity and mortality from sepsis rises.

Subjects: Acute Care; Clinical Pharmacology & Therapeutics; Gastrointestinal & Abdominal Surgery

Keywords: gentamicin; antibiotics; prescribing; compliance

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Ellen Murgitroyd is a general surgery trainee who has an interest in the management of sepsis in surgical patients.

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PUBLIC INTEREST STATEMENT

Guidelines are designed to make patient care more consistent, and to try and incorporate evidence-based medicine into daily clinical practice. Sometimes, the difficulties of incorporating guidelines into practice are not discovered until they are implemented. This paper looks at a hospital guideline incorporating gentamicin (a broad spectrum antibiotic) into the care of patients with sepsis and demonstrates that the practicality of measuring blood levels, ensuring the dose is corrected for the patients weight and the narrow therapeutic window of this drug result in non-compliance with the prescription. This can result in patient safety issues. It is hoped that this paper will encourage clinicians to look closely at guidelines and identify the pitfalls that result in failure of treatment. This can allow us to implement change and close the gap between evidence-based medicine and daily clinical practice.

1. Introduction

Hospital medicine is increasingly being driven by evidence derived from research and a move away from doing things because “we have always done it this way”. Guidelines are introduced to incorporate these changes and are designed to make patient care more consistent. The difficulties of incorporating guidelines into daily practice are often not discovered until they are implemented. This paper looks at a hospital guideline incorporating gentamicin (a broad spectrum antibiotic) into the care of patients with sepsis and demonstrates that the practicality of measuring blood levels, ensuring the dose is corrected for the patients weight and the narrow therapeutic window of this drug resulted in non-compliance with the prescription. This can lead to patient safety issues. It is hoped that this paper will encourage clinicians to look closely at guidelines and identify the pitfalls that result in failure of treatment. This can allow us to implement change and close the gap between evidence-based medicine and daily clinical practice.

Previously, prophylaxis against surgical site infections (SSIs) was often given through perioperative administration of cephalosporins. Although many antibiotics have the ability to lead to *Clostridium difficile* infection, cephalosporins are particularly associated with increased disease incidence (Slimings & Riley, 2013). Consequently, guidelines in our trust indicated use of amoxicillin, metronidazole, and gentamicin as alternatives. Subsequently, our SSI rates were documented to be increasing, likely due to a number of factors, but this prompted an audit into our use of antibiotics. Anecdotally problems with antibiotic prescribing appeared to be limited to gentamicin and vancomycin, mostly due to the monitoring regimes required. Gentamicin is used mainly for surgical procedures and treatment of sepsis; therefore, an audit of compliance with gentamicin prescription was undertaken.

Gentamicin is a widely used bactericidal aminoglycoside antibiotic with a broad spectrum of activity, with gram negative and some gram positive cover. It acts through binding to intracellular ribosomes causing inhibition of bacterial protein synthesis through disruption of translocation (Yoshizawa, Fourmy, & Puglisi, 1998). Sepsis due to *Escherichia coli*, enterobacter, klebsiella, proteus, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* may be managed with gentamicin therapy (Noone, 1978).

As gentamicin has a low toxic, therapeutic ratio and serum monitoring is used to guide dosing and prevent adverse outcomes.

Gentamicin is associated with nephrotoxicity, which is usually reversible, plus irreversible ototoxicity (Federspil, Schätzle, & Tiesler, 1976). Gentamicin is almost completely eliminated by the kidneys through glomerular filtration; therefore, drug clearance varies with renal function. Renal impairment, common in septic patients, can rapidly lead to drug accumulation. Aminoglycosides can themselves cause renal tubular cell damage, therefore preventing drug clearance and potentiating further nephrotoxic sequelae (Aronson & Reynolds, 1992; Banerjee, Narayanan, & Gould, 2012). As such it is important to measure baseline renal function prior to prescribing gentamicin, plus consider any concomitant risk factors for renal injury (pre-existing acute or chronic kidney injury, liver pathology, hypoalbuminaemia, or trough levels >2 mg/L; Naughton, 2008). Gentamicin pharmacokinetics are also affected by tissue distribution, and inter-individual variation in renal function and body composition results in initial half-life of gentamicin ranging from 0.4 to 7 h (Nahata & Crist, 1990).

The use, administration, and monitoring of aminoglycoside therapy has been the focus of extensive academic interest over the decades. Barza, Ioannidis, Cappelleri, and Lau (1996) concluded the safest method of gentamicin administration was through single daily doses, which provides lower risk of nephrotoxicity while still maintaining the efficacy of multiple daily dosing (Barza et al., 1996; Rao, Srinivasjois, Hagan, & Ahmed, 2011).

Prudent antimicrobial prescribing is essential for patient health and safety; and antibiotic stewardship is needed to prevent increasing antimicrobial resistance and *C. difficile* infection (Piacenti & Leuthner, 2013). Anecdotal evidence suggests that gentamicin prescribing and administration falls short of current guidelines, mostly due to the monitoring regimes required. This study aimed to investigate if this was the case in a large NHS teaching hospital.

2. Methods

The aim of this study was to identify whether gentamicin was being prescribed and administered correctly, according to local trust guidelines.

This study retrospectively audited gentamicin prescribing over a one-month period in Heartlands hospital, Heart of England NHS Foundation Trust (September 2009). Data were retrieved using the in-hospital electronic prescribing system. All patients prescribed gentamicin in this period were included ($n = 374$). Data were collected on demographics, admission specialty (surgical, medical, or trauma), dosing regime (stat or multidosing), number of doses administered and dosage, plus recorded reason for non-administered doses. Wards not using the electronic prescribing system were not included in the study (ITU, A&E, Paediatrics and Obstetrics & Gynaecology).

Current guidelines (see Figure 1; Table 1) for gentamicin administration and monitoring were accessible through the trust intranet. Guidelines recommended first dose based on 5 mg/kg of lean body weight (not actual body weight, to prevent toxicity), with subsequent levels taken 6–14 h later. The second dose was to be given regardless of results being available (in normal renal function), with third dose adjusted according to serum trough levels in accordance with the nomogram (Figure 2). The British National Formulary (BNF) says treatment should not exceed 7 days where possible. To avoid excessive dosage in obese patients ideal weight for height should be calculated. Once daily dosage, although more convenient, should be avoided in patients with endocarditis and burns. Concentrations should be measured after three or four doses of multiple daily dose regimens (for patients with normal renal function). Gentamicin should be avoided in pregnancy due to the risk of fetal auditory or vestibular nerve damage in the 2nd or 3rd trimester (Joint Formulary Committee L, 2010).

3. Results

A total of 374 patients were included in the audit (168 (45%) surgical; 127 (34%) medical; and 79 (21%) trauma). Of these 223 (59.6%) were prescribed once-only stat doses: 207 were administered (92.8%), and 16 were not (7.2%). The remaining 151 patients were prescribed gentamicin on a multi-dose prescription (40.4%): of these 35 (23%) received doses consistent with guidelines.

In total 41 patients (11%) did not receive a single dose. Of patients prescribed multidose regimens of gentamicin, 25 (16.6%) received zero doses, 41 (27.2%) patients one dose, 50 (31.1%) patients two doses, and 35 (23.2%) patients greater than three doses (see Figure 3).

3.1. Prescription issues

One patient was prescribed gentamicin despite being allergic to gentamicin. No doses were given, and the prescription was subsequently discontinued. Five prescriptions (1.3%) exceeded the BNF recommended 7 doses, ranging from 8 to 40 doses (three patients were being treated for infective endocarditis and had >30 doses). There were 37 as required (PRN) prescriptions, with no clear indication documented. As patient weights were not recorded electronically, we were unable to assess how many of these doses were adequately prescribed according to lean body weight.

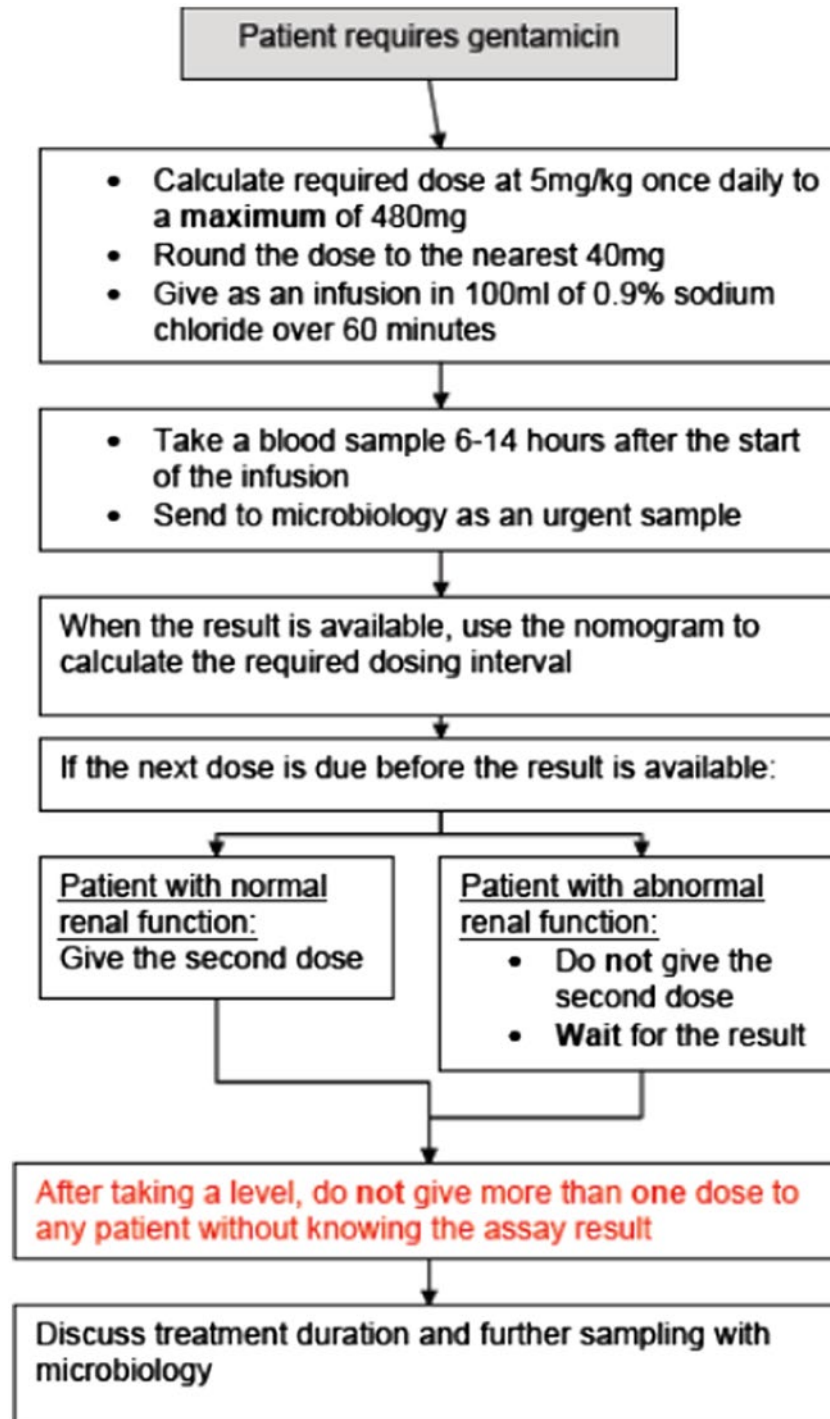
4. Discussion

Our study has highlighted the wide variability in gentamicin prescription and administration, which often falls short of current guideline recommendations.

4.1. Prescription issues

The number of patients receiving over seven doses of gentamicin is small (1.3%) and the data suggest these patients were dosed according to levels taken (doses were adjusted) so this was likely to be intentional. Although clinical need allows for longer term treatment, 40 doses are unlikely to be justified. Long-term treatment was observed in a minority of patients and therefore is not as significant as the numbers not receiving prescribed multidose regimes.

Figure 1. Gentamicin prescribing and administration guidelines.

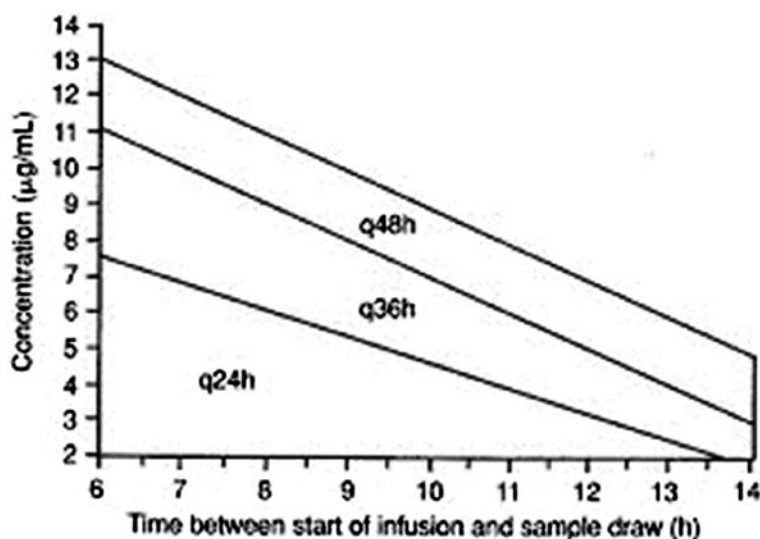


Patient weight was not recorded on electronic prescribing, this is not mandatory and it may have been recorded on paper nursing records or the main clinical record; however, estimating weight is a common practice, and the impact of this is unclear without gentamicin levels being available. Gentamicin dosing should be based on lean weight for height and not actual weight—which anecdotally is rarely calculated.

Table 1. Trust antibiotic guidelines: indications for gentamicin

Condition	Dosing regime	Concurrent antibiotics
Endoscopic prophylaxis in neutropenic patients	Stat	
Upper and lower GI surgery, vascular surgery, and thoracic surgery—if penicillin allergy	Stat	
Urology—risk of bacterial endocarditis	Stat	
Urology—endoscopic, laparoscopic, and percutaneous nephrostomy	Stat	
Urology—open surgery if penicillin allergy	Stat	Metronidazole
Trauma and orthopaedics—elective surgery involving implants or neck of femur fracture (hemiarthroplasty)	Stat	Flucloxacillin
UTI with systemic symptoms	5 mg/kg—max 480 mg	Co-amoxiclav
Severe sepsis of unknown origin	5 mg/kg—max 480 mg	Amoxicillin, metronidazole
Biliary sepsis—acute cholecystitis, acute cholangitis; non-septic secondary peritonitis; acute diverticulitis; appendicitis	5 mg/kg—max 480 mg	Amoxicillin, metronidazole
Diffuse peritonitis	5 mg/kg—max 480 mg	Tazocin

Figure 2. The Hartford nomogram.



4.2. Administration issues

The data show that 93% of stat gentamicin doses were administered, while 17% of patients on a prescribed multidosing regime did not receive a single dose of gentamicin.

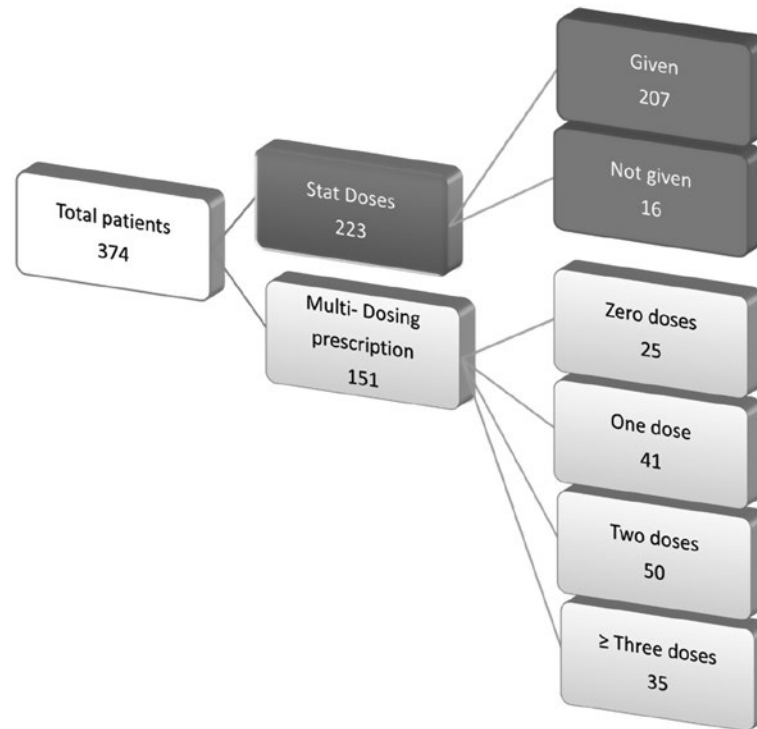
Informal discussion with clinical staff identified the most common reason for non-administration was lack of IV access; however, this would need formal evaluation.

Of patients receiving gentamicin, 40% were on multidosing regimes; however, 27% of patients actually only received a single dose of gentamicin, and hence were undertreated. Further discussion with clinical staff identified possible reasons for this as gentamicin levels not being taken, or results not being available before the second dose was due—despite clinical guidelines advising patients with normal renal function are to be given the second dose regardless.

4.3. Implications of non-compliance with guidelines

Woolf, Grol, Hutchinson, Eccles, & Grimshaw discuss the benefits of clinical guidelines and state that the “principal benefit is to improve the quality of care received by patients” (Woolf et al., 1999) and there are studies which prove that this can occur (Grimshaw & Russell, 1993), however guidelines are

Figure 3. Summary of gentamicin administration in a one-month period.



revised and updated because it is recognized that evidence is updated as research progresses and problems encountered with implementation of guidelines into daily practice are addressed. Well-developed clinical guidelines can improve the quality of care for our patients, but to ensure they are well developed, and consider atypical presentations (to allow malleability of guidelines in uncommon situations), we must be willing to audit our practice and recognize new developments and how they affect current guidelines.

In this study, the major problem with significant clinical implications is the fact that under-dosing appears common. Less than a quarter of our patients on multidose regimes received correct antibiotic therapy. The question we need to ask is does under-dosing gentamicin lead to significant increases in morbidity and mortality? Timely and appropriate antibiotics are at the core of sepsis management, in both medical and surgical settings. Initiation of appropriate antibiotics within an hour from presentation is significantly associated with decreased patient mortality (Gaeski et al., 2010). The mortality from gram negative rod bacteraemia is significantly reduced with appropriate antibiotic therapy (Bryant, Hood, Hood, & Koenig, 1971). Early establishment of adequate peak gentamicin levels is significantly associated with decreased mortality rate compared to sub-therapeutic plasma levels (Moore, Smith, & Lietman, 1984). Additionally, correct antibiotic therapy reduces length of inpatient stay (Battleman, Callahan, & Thaler, 2002).

4.4. Reasons for non-compliance

This study highlights clear patient safety issues, with sub-therapeutic antibiotic courses leading to undertreatment of sepsis; plus extended drug courses exposing the patient to potentially toxic side effects. Adverse drug events, defined as injuries to patients secondary to drug administration, are the most common cause of harm to hospitalized patients, and are often preventable (Bates, Cullen, Laird, & Al, 1995). Numerous reasons have been highlighted as causal in prescription errors. Lack of knowledge and training in prescribing, lack of familiarity with the drug or patient, time pressure and heavy workload have all been identified as reasons behind prescribing errors (Dean, Schachter, Vincent, & Barber, 2002).

Reasons for non-administration in this study were documented most frequently as “other” but included lack of IV access (no cannula or cannula being used for other drugs/fluid) and trough levels not available (level not taken, taken late, available and not actioned, levels not required but guidelines misinterpreted, and second dose not given prior to results being available).

This study underlines the need for clearer documentation as to indication for antibiotic prescription, and why subsequent doses not given. It may be that microbiology results indicated organisms were resistant to gentamicin, therefore cessation of the drug was entirely appropriate. However, a number of reasons may have contributed to poor adherence to guidelines. Doctors may be apprehensive using gentamicin due to known toxic effects of the drug; gentamicin doses may be missed due to levels not being taken within correct time period and difficulty bleeding the patient; drug dose may not be altered appropriately according to plasma gentamicin level; and poor communication with nursing staff may lead to confusion regarding dosing alteration. These findings are not just limited to our trust, with suboptimal aminoglycoside prescribing common despite easy access to prescribing guidelines (Leong, Busing, Richards, Robertson, & Street, 2006; Shrimpton et al., 1993).

This study was not able to investigate what level of training the prescriber was. Junior staff, at the time of audit, were relatively inexperienced (one month into post, for many following graduation). Therefore, more could be invested into education at both undergraduate and postgraduate levels, to improve departmental confidence in safe prescribing and drug monitoring. A teaching session was given at the foundation doctors teaching session, the study was repeated after this (during the last month of foundation doctors rotation) and compliance was still in the region of 20%. Additionally, this study was not aimed at investigating patient outcome; however given results would be pertinent to investigate this in future.

4.5. Limitations

This study looks at a single antibiotic, over a limited time period, without patient outcome measures, but despite this raises some important questions.

Without the recorded weight (or predicted lean body weight), and the laboratory trough levels, under-dosing cannot be definitively measured and is only suggested by the data.

4.6. Clinical relevance

Should we be using a drug with such significant side effects and perceived complexities in monitoring and administration, if as this study suggests, it is not being used effectively? Gentamicin should be used for selected patients, when monitoring can be ensured. Using it widely for multiple conditions leads to high numbers of patients requiring close monitoring. This results in difficulty ensuring compliance leads to non-effective underdosing. An antibiotic with multiple routes of administration, wider therapeutic index, and not requiring dose monitoring is more likely to be given appropriately, and therefore more effective in treating infection and sepsis.

4.7. Further studies

Future work would include re-audit of gentamicin prescribing following change in local guidelines. Additionally patient outcome, and length of inpatient stay following gentamicin prescription could be investigated. A survey of clinical staff to evaluate understanding of current guidelines will be undertaken and additional training provided if necessary. Further study would ideally also include laboratory levels and lean body weight.

An additional factor to consider is the inexperience of junior doctors during this time period (August). Data can be compared with that of the following July to assess the significance of this.

5. Conclusion

Gentamicin is a useful antibiotic in the treatment of gram-negative infection; however, current use often falls short of local guideline recommendation. This may be due to a number of reasons including difficulty in drug monitoring, and apprehension amongst prescribers in the use of gentamicin,

and loss of intravenous access. Failure of administration of appropriate antibiotic cover has a negative effect on in-patient stay, morbidity, and mortality; therefore, this trend must be reversed to prevent multiple poor outcomes and promote patient safety.

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Competing interests

The authors declare no competing interest.

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