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Review

Single centre observational study on antibiotic prescribing adherence to clinical practice guidelines for treatment of uncomplicated urinary tract infection

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Abstract *Background:* Urinary tract infections are one of the most common infections encountered in ambulatory care and the inpatient setting. Antibiotic resistance is a growing concern in healthcare worldwide and has been described by the World Health Organisation as one of the key global health issues facing our generation. The objective of this study was to evaluate antibiotic prescribing adherence to national therapeutic guidelines for patients with uncomplicated urinary tract infection.
Methods: A single centre, retrospective study of patients with uncomplicated urinary tract infections presenting to the Gold Coast University Hospital in May 2015. Infections were categorised according to male cystitis, female cystitis, mild pyelonephritis and severe pyelonephritis, with antibiotic prescribing assessed against the Australian Therapeutic Guidelines.
Results: 103 patients met the inclusion criteria, 47 (45.6%) received treatment that adhered to the Australian Therapeutic Guidelines. Eight (7.8%) did not adhere but the decision of non-adherence was justified. 48 (46.6%) received treatment that did not adhere to the Australian Therapeutic Guidelines. The most common reason for non-adherence were incorrect dose followed by incorrect duration. There was a lack of fluoroquinolone use in this study.
Conclusions: These results highlight the poor adherence to guidelines in uncomplicated urinary tract infection. Non-adherent duration of treatment is likely contributed by inappropriate number of tablets being dispensed in boxes.

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Highlights

- 45.6% of patients with uncomplicated urinary tract infections received nonadherent treatment.
- Incorrect dose, followed by incorrect duration of therapy were the most common reasons for non-adherence.
- When duration of therapy was non-adherent, a common factor was an inappropriate quantity of tablets dispensed.
- Fluoroquinolone use was significantly lower compared to similar non-Australian studies.
- Antibiotic stewardship at the hospital level is important for improving antibiotic prescribing adherence.

Introduction

Antibiotic resistance is a growing challenge in healthcare worldwide. Antibiotic resistance crisis has been attributed to the overuse and misuse of these medications. Previous epidemiological studies have demonstrated a direct relationship between antibiotic consumption and the emergence of resistant bacteria strains [1].

Managing the emergence and increasing resistance to antibiotics in hospitals and the community has become an urgent national problem for Australia and the rest of the world. The World Health Organisation (WHO) described antimicrobial resistance as one of the key global health issues facing our generation [2]. Use of antimicrobials in Australian Hospitals is relatively high compared to other countries shown in the figure below [3] (Fig. 1).

In 2015, the Department of Health and the Department of Agriculture in Australia developed the National Antimicrobial Resistance Strategy. Their goal is to minimise the development and spread of antimicrobial resistance in Australia [5]. The Antimicrobial Use and Resistance in Australia (AURA) project, a surveillance program, was also created from this strategy. Data from the first report on antimicrobial resistance, released by the AURA project, demonstrated that in Australian Hospitals, 21.9% of prescriptions were considered inappropriate and that 23.3% were non-compliant with national or local guidelines [3]. The 2017 AURA report observed that the five most commonly prescribed antibiotics were amoxycillin-clavulanate, cephazolin, amoxycillin, flucloxacillin and doxycycline [3]. A key issue identified by the report was a misuse of cephalexin, for the treatment of urinary tract infections as well as other indications such as surgical prophylaxis [3]. The antibiotic most widely prescribed appropriately include narrow spectrum antibiotics, such as trimethoprim [3].

Improving prescribing and limiting resistance of organisms with antimicrobial stewardship consists of coordinated interventions designed to promote the optimal use to antibiotic agents, including their choice, dosing, route, and duration of administration [4]. The Australian Therapeutic Guidelines is an independent comprehensive prescribing guide initially developed in 1978 by a group of experts in response to the worrying and merging problem of antibiotic resistance. The Therapeutic guidelines is recognised in Australia as the prime source of accurate and practical treatment guidelines for practitioners [6]. Another coordinated intervention is government regulation to control the use and supply of antibiotics. The control of fluoroquinolone prescribing has been demonstrated in Australia with the national pharmaceutical subsidy scheme, regulation not permitting use in food producing animals and hospitals that restrict their use. Most Australian hospitals restrict fluoroquinolones, reserving their use for the treatment of drug resistant microbials [3].

Urinary tract infections (UTIs) are one of the most common indications for antibiotic prescription in Australia. According to the AURA 2017 report, 21.2% on antibiotic prescriptions were inappropriate [3]. Although these infections are common, not all patients are

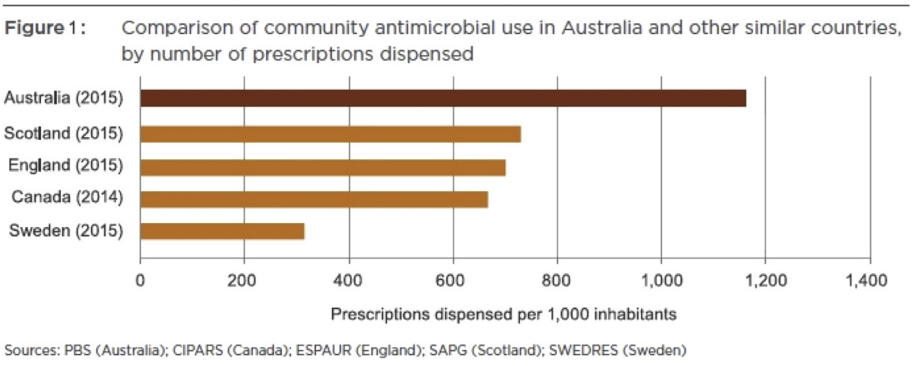

Figure 1 Comparing antibiotic use in Australia and other countries.

prescribed an antibiotic regime adherent to the Australian Therapeutic Guidelines [7]. The primary objective of this analysis was to evaluate the adherence to national guidelines of antibiotic selection, dosing and duration of therapy for patients admitted to Gold Coast University Hospital diagnosed as having an uncomplicated urinary tract infection. This study assesses the adherence of antibiotic therapy using a standardized method for duration of therapy, dosage, dosage interval, and choice of antibiotic drug.

Method

Patient selection and study design

We identified all patients at Gold Coast University Hospital, a tertiary hospital in May 2015.

299 patients were identified as having a urinary tract infection via discharge code of urinary tract infection. Inclusion criteria included all bacteriuria's with a positive urine cultures and symptoms or clinical signs from medical records suggestive of urinary tract infection.

These symptoms included dysuria, increased frequency of urinary of urination, hesitancy to urinate, urinary incontinence, nausea, confusion, abdominal pain, and rigors.

The patients would be included as either cystitis or pyelonephritis based on documentation in medical records. In situations where it was not documented clearly whether the patient had cystitis or pyelonephritis, they would be classified based on description of symptoms.

Cystitis symptoms would consist of dysuria, frequency, urgency, suprapubic pain, and/or haematuria, with the absence of pyelonephritis symptoms. Pyelonephritis symptoms would consist of above symptoms with fever ($>38\ ^{\circ}C$), chills, flank pain, and costovertebral angle tenderness [8].

Patients were excluded if they had complicated urinary tract infections such as patients who were pregnant, urinary tract obstructions, renal transplant patients, immunosuppressed and those with presence of indwelling catheter, stent, nephrostomy tube or urinary diversion. Patients with concomitant infections from any organism (bacterial or viral pneumoniae, skin infection etc.) were excluded based on complaints or clinical signs from medical records. Patients who were already on antibiotics at presentation to Gold Coast University hospital, under the age of 18 (paediatric group), and/or patients with recurrent urinary tract infections or recent urinary tract infection within the past month due the possibility of treatment failure from previous infection were also excluded.

After inclusions, the patients were grouped into either:

- Acute cystitis in non pregnant women
- Acute cystitis in men
- Acute pyelonephritis - mild infection
- Acute pyelonephritis - severe infection

Primary outcome

The primary outcome was prescribing adherence to guidelines for management of uncomplicated urinary tract infection to choose of medication, duration and dose. For those prescribers who did not follow local guidelines, the non-adherence was justified only if the patient had a previous intolerance/allergy to recommended antibiotic or an alternative antibiotic was recommended by microbiology because of resistance patterns. This group would be classified as a justified non-adherence.

Data collection and analysis

Data was collected retrospectively by reviewing patient electronic medical charts and laboratory data. The collection of data was completed by the authors (TP and GM).

Data collected included patient gender, age, symptom, and confirmed urine microscopy, culture and sensitivities. With prescribing, data was collected for choice of antibiotic, route, duration, dose and frequency. Clinician directed antibiotic treatment was compared to the Australian Therapeutic Guideline empiric antibiotic regime options which can be chosen between at clinician digression (for full regime details refer to Tables 1—3) [6]. Furthermore, justified antibiotic choice included consideration of previous allergy/intolerances or if the microbiology department had recommended another antibiotic in the case [6].

Descriptive statistics was used to quantitate analysis of data. Justified non-adherences and non-adherences were all assessed individually by authors (TP and GM) for reasons of non-adherence (dose, duration, and/or frequency).

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Table 1 Australian Therapeutic Guidelines empiric antibiotic regime for acute cystitis in nonpregnant women.

Oral trimethoprim 300 mg daily for 3 days	OR
Oral cephalexin 500 mg twice daily for 5 days	OR
Oral Amoxycillin/clavulanate 500/125 mg twice daily for 5 days	OR
Oral nitrofurantoin 100 mg twice daily for 5 days	OR

Table 2 Australian Therapeutic Guidelines empiric antibiotic regime for acute cystitis in men.

Oral trimethoprim 300 mg daily for 7 days	OR
Oral cephalexin 500 mg twice daily for 7 days	OR
Oral Amoxycillin/clavulanate 500/125 mg twice daily for 7 days	OR
Oral nitrofurantoin 100 mg twice daily for 7 days	OR

Table 3 Australian Therapeutic Guidelines empiric antibiotic regime for mild pyelonephritis.

Mild pyelonephritis (low-grade fever, no nausea or vomiting and/or oral step down for severe pyelonephritis)	Oral amoxycillin/clavulanate 875/125 mg, twice daily for 10—14 days	OR
	Oral cephalexin 500 mg, four times daily for 10—14 days	OR
	Oral trimethoprim 300 mg, daily for 10—14 days	OR
Severe pyelonephritis[a]	Intravenous gentamicin (renal and weight adjusted dosing) + Intravenous amoxy/ampicillin 2 g four times daily	OR
If gentamicin is contraindicated or relevant precautions preclude its use as a single drug, use:		
	Intravenous ceftriaxone 1 g daily	OR
	Intravenous cefotaxime 1 g three times daily	OR

[a] Duration of antibiotics for severe pyelonephritis was still 10—14 (including oral step down to mild pyelonephritis regimes and intravenous regimes) but was allowed for up to 21 days if poor clinical response to antibiotic therapy.

Results

A total of 103 of 296 patients met the inclusion criteria. Of these patients 47 (45.6%) received treatment that adhered to the Australian Therapeutic Guidelines. Eight (7.8%) did not adhere but the decision of non-adherence was justified. 48 (46.6%) received treatment that did not adhere to the Australian Therapeutic Guidelines. The non-adherences were either due to wrong dose, duration, frequency or antibiotic choice (See Fig. 2).

Of these 48 non-justified non-adherences, incorrect dose was the most common reason (24/48). All the incorrectly dosed patients were diagnosed as cystitis (with absence of fever, chills, flank pain or costovertebral tenderness), but discharged on the mild pyelonephritis dose of amoxycillin + clavulanate dose 875/125 mg BD and cystitis duration of five days. Incorrect duration (13/48) was the second most common non-adherence with the majority being long durations (9/13). Other non-adherences included incorrect frequency (7/48), antibiotic choice (3/48), and dose and duration (1/48). All seven incorrect dose frequencies were observed when clinicians prescribed cephalexin. Either an increased frequency of three times daily (3/7) or four times daily (4/7) was prescribed, rather than the recommended twice daily dose. Of the 14 incorrect duration non-justified non-adherence cases, nine were due to a longer than recommended duration. Seven cases were due to a prolonged duration of trimethoprim, which ranged from five to 11 days total. The three non-justified non-adherent antibiotic choice cases were prescribed cephazolin (1/3) and amoxycillin without clavulanate (2/3). There was one case of incorrect dose and duration where the patient received inappropriately short duration and low dose antibiotic therapy for pyelonephritis.

Of the eight justified non-adherences, all were recommendations by the microbiologist or infectious disease physician based on microbe grown or sensitivities. Four of the justified non-adherences grew Pseudomonas which were the only four patients in the study prescribed fluoroquinolones.

Figure 2 Selection of participants for the retrospective, single centre study.

The most common characterisation of adherence was use of trimethoprim in male and female cystitis (as seen in Table 4).

Discussion

In our study 45.6% of patients received urinary tract infection treatment that adhered to the Australian Therapeutic Guidelines. 7.8% receiving non-adherent treatment that was justified due to microbial resistance or previous antibiotic allergy/intolerances. The main reason for non-adherence to guidelines was incorrect dose in cystitis where the mild pyelonephritis dose of amoxycillin + clavulanate 875/125 mg BD was prescribed with the cystitis duration of five days. The doses of all other antibiotics prescribed were all correct. It is unclear why there were so many patients prescribed the higher dose of amoxycillin + clavulanate, one study suggested overprescribing could be driven by fear of undertreatment [9]. Also, we are not aware of any studies demonstrating any increased risk to antibiotic resistance with a higher dose of amoxycillin.

The second most common reason for non-adherence was incorrect duration in 13 cystitis patients. Nine of these incorrect durations were due to duration being too long, seen in trimethoprim and cephalexin. There were no incorrect durations for amoxycillin + clavulanate which is only sold in a box of ten, which would leave the patient with no spares tablets when prescribed a twice daily dose for five-day duration. All the incorrect durations were for female patients for cystitis. Trimethoprim is sold in a box of seven, which leaves spare tablets when prescribed a once daily dose for duration of three days in female cystitis. Cephalexin is sold in a box of 20, which also leaves spare tablets when prescribed a twice daily dose for five days in female cystitis. When a box is sold with 20 tablets, the doctor may prescribe a twice daily dose for duration of ten days rather than the recommended five days in female cystitis. In a previous Dutch study, the authors identified one of the barriers to follow the guidelines was the appropriateness of boxes of antibiotics for short course treatments [10]. Another potential reason for longer durations could be due to the deeply embedded idea from doctors and patients that antibiotic courses should always be completed to minimise resistance. The idea that stopping antibiotic treatment early encourages antibiotic resistance is not supported by evidence, whereas taking antibiotics for longer than necessary increases the risk of resistance [9]. If trimethoprim were also sold in boxes of three and cephalexin in boxes of ten, this could potentially lessen the barrier for non-adherent duration prescribing for practitioners.

There are several limitations to this study that warrant discussion. The study period only spanned one month with results potentially varying when different practitioners rotate through the hospital during the year. A longer study would potentially have minimised individual errors or differing practice styles. This short study period also does not allow assessment of prescribing trends over time. With the study setting based in a large academic tertiary hospital, there are likely different levels of prescriber training and experience between departments. This is more a strength of this study, minimising potential bias that may occur within a single department. Another limitation of the study was with accuracy of diagnoses being made for urinary tract infection. In some cases, the clinical notes were not clear for the authors to confidently determine if the patient had cystitis or mild pyelonephritis. If the patient was prescribed a mild pyelonephritis dose and duration, it was assumed that the diagnosis was mild pyelonephritis. In comparison, if a patient was prescribed a cystitis dose but a mild pyelonephritis duration, it was determined that the prescriber was non-adherent to guidelines. Since the study primary outcome is focused on prescribing adherences, the potential effect of incorrect diagnoses is minimalised with this approach.

We found a high rate of adherence to guidelines for treatment of urinary tract infection in this study in comparison with previous international studies where overall adherences ranged from 17.7 to 36.9% [11—15]. A potential reason for this may be due to previous studies focussing on a single population setting such as the primary care physician, emergency department or an outpatient clinic. An emergency department or primary care physician in general practice are both different settings to an adult tertiary hospital. Emergency doctors and primary care physicians usually need to make quick treatment decisions with incomplete information and limited opportunity to follow up.

The results of this study are similar to the recent 2015 Hospital National Antimicrobial Prescribing (NAP) Survey in

Table 4 Summary of Australian Therapeutic Guideline for urinary tract infection antibiotic regimes and details of adherent antibiotic prescriptions.

Urinary tract infections	Antibiotic regime	Quantity
Male cystitis	Trimethoprim 300 mg orally, daily for 7 days	7
	Amoxycillin + clavulanate 500/125 mg orally, 12-hourly for 7 days	1
Non-pregnant female cystitis	Trimethoprim 300 mg orally, daily for 3 days	9
	Cephalexin 500 mg orally, 12-hourly for 5 days	8
	Amoxycillin + clavulanate 500/125 mg orally, 12-hourly for 5 days	2
Mild pyelonephritis	Amoxycillin + clavulanate 875/125 mg orally, 12-hourly for 10—14 days	6
	Cephalexin 500 mg orally, 6-hourly for 10—14 days	4
	Trimethoprim 300 mg orally, daily for 10—14 days	4
Severe pyelonephritis	Gentamicin IV PLUS amoxy/ampicillin 2 g IV 6-hourly	6
Total		47

Australia, where 55.9% of prescriptions overall were compliant with Australian Therapeutic Guidelines. Although this overall compliance included all other types of infections [9]. In addition to compliance, the Hospital NAP survey also assessed appropriateness with a rate of 77% in cystitis (158/205). Antimicrobial prescription may still be deemed appropriate if it did not optimally follow the Australian Therapeutic Guidelines but was still considered a reasonable alternative for the likely causative or cultured pathogens.

Half the non-adherences in this study were due to the 875/125 mg dose of amoxycillin + clavulanic acid being prescribed rather than the recommended 500/125 mg dose. Based on the Hospital NAP survey criteria, these incorrect dose non-adherences would be considered appropriate with overall rates of appropriateness for cystitis prescribing almost identical (77.7%).

An interesting finding in this study was the lack of fluoroquinolones being prescribed. A previous single centre study in America described fluoroquinolone use as the most common reason for non-adherence in cystitis which occurred in 97.6% of patients. The study suspected this may be due to the Infectious Disease Societies' older guidelines in 1999 which recommended fluoroquinolones as first line therapy in cystitis. None of the non-adherences in this study were due to fluoroquinolones being prescribed. Four of the eight (50%) justified non-adherences were due to fluoroquinolones use. All fluoroquinolone use was based on microbiology recommendations and sensitivities for Pseudomonas spp. which is naturally resistant to penicillin and majority of related beta-lactam antibiotics. The likely reason for the low fluoroquinolone usage rates is due to strategies to restrict use in most Australian Hospitals. In this study, fluoroquinolone use was determined by the hospital's antimicrobial stewardship group which determined that fluoroquinolones were only available for infections caused by Pseudomonas and certain multidrug-resistant bacteria after approval from the microbiologist or infectious disease specialist. This study demonstrates the success of an hospital antimicrobial stewardship committee and effects of restricting the use of certain antibiotics at the hospital level. The AURA 2017 report has shown that fluoroquinolone usage rates have continued to decrease Australia wide since 2011 by 9.7%. Despite reduced usage, the rates of resistance to fluoroquinolones in *Escherichia coli* and *Klebsiella pneumoniae* are gradually increasing. In comparison with most European countries, rates of fluoroquinolone resistance are low in Australia [3,16].

Conclusion

We found 46.6% of patients with uncomplicated urinary tract infection were treated with antibiotics that did not adhere to the Australian Therapeutic Guidelines. There was a lack of fluoroquinolone use in comparison to similar non-Australian studies, representative of the Hospital's restrictions on fluoroquinolones and likely prescribing attitudes within Australian due to the national pharmaceutical subsidy scheme and government regulations. The most common characterisation of non-adherence was the incorrect dose of antibiotic namely the overuse of the pyelonephritis dose of amoxycillin + clavulanate for the treatment of cystitis. This was followed by non-adherent duration which was only seen in antibiotics dispensed in boxes with an inappropriate number of tablets for short course treatments. The appropriateness of the dispensed boxes of antibiotics is likely relevant to the non-adherent durations. Larger population studies comparing effect of duration adherences based on region appropriateness of boxes of antibiotics are important. This could potentially encourage changes at the government regulatory level to limit the amount of antibiotic dispensed based on indication.

Authorship statement

TP — developed analysis plan, analysed data, revised paper.
GM — analysed data, revised paper.
FH — developed analysis plan, revised paper, final approval.

Conflicts of interest

Nil conflicts to declare.

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Provenance and peer review

Not commissioned, internally peer reviewed.

Ethics

This study was reviewed and approved by the Ethics Review Board at the Gold Coast University Hospital.

References

[1] The antibiotic alarm. Nature March 2013;495:141.
[2] World Health Organisation. Antimicrobial resistance: global report on surveillance. June 2014. http://apps.who.int/iris/bitstream/10665/112642/1/9789241564748_eng.pdf.
[3] Turnidge John, Binns Phillipa, Cruickshank Marilyn, Firman Jenny, Heaney Aine, McKenzie Duncan, et al. AURA 2017: second Australian report on antimicrobial use and resistance in human health. Sydney: ACSQHC; 2017. http://www.safetyandquality.gov.au/antimicrobial-use-and-resistance-in-australia/resources-page/.
[4] Barlam T, Cosgrove S, Abbo L, MacDougall C, Schuetz A, Septimus E, et al. Implementing an antibiotic stewardship program: guidelines by the infectious diseases society of America and the society for healthcare epidemiology of America. Clin Infect Dis J May 2016;62(10).
[5] Commonwealth of Australia. National Antimicrobial Resistance Strategy 2015—2019 — Responding to the treat of antimicrobial resistance. June 2015. http://www.agriculture.gov.au/SiteCollectionDocuments/animal-plant/animal-health/amr/responding-threat-antimicrobial-resistance.pdf.
[6] Therapeutic Guidelines Ltd. Urinary tract infections. November 2014. https://tgldcdp.tg.org.au/etgAccess.

[7] Bent S, Nallamothu B, Simel D. Does this woman have an acute uncomplicated urinary tract infection? JAMA J Am Med Assoc May 2002;287(20). https://doi.org/10.1001/jama.287.20.2701.
[8] Wimmer B, Johnstone L, Mackay C, Harris E, Mullen A. Antibiotic prescribing for urinary tract infection in hospices in Scotland. Eur J Palliat Care 2014;21(1).
[9] Zatorski C, Zocchi M, Cosgrove S, Rand C, Brooks G, May L. A single center observational study on emergency department clinician non-adherence to clinical practice guidelines for treatment of uncomplicated urinary tract infections. BMC Infect Dis 2016;16:638.
[10] Llor C, Rabanaque G, Lopez A, Cots J Maria. The adherence of GPs to guidelines for the diagnosis and treatment of lower urinary tract infection in women is poor. Fam Pract 2011.
[11] Hecker M, Fox C, Son A, Cydulka R, Siff J, Emerman C, et al. Effect of a stewardship intervention on adherence to uncomplicated cystitis and pyelonephritis guidelines in an emergency department setting. PloS One 2014;9(2).
[12] Kim M, Lloyd A, Condren M, Miller MJ. Beyond Antibiotic selection: concordance with IDSA guidelines for uncomplicated urinary tract infections. Springer Science; 2015.
[13] Cheng A, Turnidge J, Collignon P, Looke D, Barton M, Gottlieb T. Control of fluoroquinolone resistance through successful regulation, Australia. Emerg Infect Dis 2012;18(9).
[14] Lugtenberg M, Burgers JS, Zegers-van Schaick JM, Westert GP. Guidelines on uncomplicated urinary tract infections are difficult to follow: perceived barriers and suggested interventions. BMC Fam Pract 2010. https://doi.org/10.1186/1471-2296-11-51.
[15] Llewlyn M, Fitzpatrick J, Dawrin E, Tonkin-Crine S, Gorton C, Paul J, et al. The antibiotic course has had its day. BMJ 2017. https://doi.org/10.1136/bmj.j3418.
[16] Results of the 2015 Hospital National Antimicrobial Prescribing Survey. Australian commission on safety and quality in health care. 2016. https://www.naps.org.au/Resources/Antimicrobial-prescribing-practice-in-Australian-hospitals-Results-of-the-2015-National-Antimicrobial-Prescribing-Survey.pdf.