Urinary tract infection in children at Victoria Hospital, a district hospital in Cape Town, South Africa

By

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The minor dissertation is presented in publication-ready format using the South African Medical Journal instruction to authors guidelines. It has not been submitted for publication.

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Table of Contents

List of Appendices……5
List of Tables……5
List of Figures……...5
Abbreviations……....6
Abstract……7
Publication-ready Manuscript……...……....8
References……17

List of Appendices

Data capture sheet
Human Research Ethics Committee approval
South African Medical Journal author guidelines

List of Tables

Description	Page Number
1. Antibiotic susceptibility of Enterobacterales isolated	13
2. Initial empirical antibiotic treatment of study participants (N=78)	13

List of Figures

Description	Page Number
1. Selection of urinary tract infection episodes for analysis	20

Abbreviations

ART	Antiretroviral therapy
AST	Antibiotic susceptibility testing
CFU/mL	Colony forming units per milliliter
ESBL	Extended spectrum beta-lactamase
HIV	Human immunodeficiency virus
HLP	Hospital Level Paediatrics
HREC	Human Research Ethics Committee
IQR	Interquartile range
IV	Intravenous
NHLS	National Health Laboratory Service
OECD	Organisation for Economic Co-operation and Development
PHC	Primary health care
SA	South Africa
STG/EML SA HLP	Standard Treatment Guidelines and Essential Medicines List for South Africa Hospital Level Paediatrics
STG/EML SA PHC	Standard Treatment Guidelines and Essential Medicines List for South Africa Primary Health Care Level
STG/EML	Standard Treatment Guidelines and Essential Medicines List
STG	Standard Treatment Guidelines
ug/mL	Micrograms per milliliter
UTI	Urinary tract infection

Abstract

Background: Urinary tract infections (UTI) are one of the most common bacterial infections in childhood, with the potential to cause acute and long-term complications. Diagnosing UTI in children is often challenging due to non-specific symptoms, difficulty in collecting sterile specimens, and culture results only becoming available after 24-48 hours, necessitating initiation of empiric antibiotic therapy. Recent data on the epidemiology and antibiotic susceptibility profile of community-acquired bacterial UTI in children in Cape Town is lacking.
Objectives: To describe the clinical profile and organisms including antibiotic susceptibility testing (AST) results in children <10 years of age with community-acquired, culture-confirmed bacterial UTI attending Victoria Hospital, Cape Town. To compare the AST findings with the current South African (SA) Hospital Level Paediatric Standard Treatment Guidelines (STG) which recommend oral or parenteral amoxicillin/clavulanic acid as first-line empiric treatment for children with UTI, with ceftriaxone included as an alternative for neonates or acutely ill infants.
Methods: A retrospective review of medical records and laboratory results of children <10 years of age who had a urine specimen submitted for culture and AST to the National Health Laboratory Service from Victoria Hospital between 1 February 2016 – 31 July 2019 was performed. The study definition of a culture-confirmed bacterial UTI is modified from the SA STG guidelines: (1) any culture from a suprapubic aspirate, (2) culture of $>10^4$ colony forming units (CFU)/mL of a single organism from a catheter urine specimen, (3) culture of $>10^5$ CFU/mL of a single organism from a mid-stream clean catch specimen or if the urine sampling technique was not indicated in the laboratory or medical records. Descriptive statistics were used to analyse the data.
Results: From 528 urine specimens submitted, 89 specimens met the study definition of bacterial UTI and were included in the microbiological analysis. Seventy-eight children with available medical records were included in the demographic and clinical analysis. Median (interquartile range) age was 25 (0;117) months and 58% were female. One or more non-specific features of systemic illness were reported in 65% of children, and 51% had at least one symptom specific to the urinary system. *Enterobacterales* accounted for 99% of the organisms cultured (85% were *Escherichia coli*) and their susceptibility was amoxicillin/clavulanic acid (58%), cefuroxime (84%), third and fourth generation cephalosporins (88%), ciprofloxacin (94%), gentamicin (86%) and nitrofurantoin (90%). Eleven (12%) isolates were extended spectrum beta lactamase-producing organisms but no carbapenem-resistant organisms were isolated.
Conclusion: Although this study did not evaluate clinical outcomes of children, the AST finding that only 58% of *Enterobacterales* isolates were susceptible to the recommended empiric treatment with amoxicillin/clavulanic acid raises the concern that children may not be receiving appropriate treatment for UTI. Further research is needed on the antibiotic susceptibility profile and clinical outcome of children treated for UTI in order to inform appropriate empiric antibiotic treatment recommendations.

Urinary tract infection in children at Victoria Hospital, a district hospital in Cape Town, South Africa

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Urinary tract infections (UTI) are common bacterial infections in childhood, affecting 8% of girls and 2% of boys under 7 years of age [1-4], with the potential to cause severe acute and long-term complications including sepsis, renal scarring and chronic kidney disease.[2] For this reason, early diagnosis and prompt and effective therapy is needed.[4] Diagnosing UTI in young children is challenging due to non-specific symptoms and signs, and difficulty in collecting sterile specimens particularly in non-toilet trained children, of which the most reliable method remains controversial.[2] Urine culture is the standard method of confirming the diagnosis, however it takes 24–72 hours to detect bacterial growth and determine antibiotic susceptibility testing (AST) results; consequently antibiotic treatment is frequently started without a confirmed diagnosis or AST results.[2] The choice of an empirical antibiotic is based on the likely antibiotic susceptibility of common bacteria causing UTI in children. If urine culture and AST is performed and yields a positive and clinically compatible result, antibiotics must be adjusted to target the specific bacteria causing the UTI and de-escalated to the narrowest spectrum antibiotic available where appropriate. The Standard Treatment Guidelines and Essential Medicines List (STG/EML) for South Africa (SA) Primary Healthcare (PHC) Level 2020 Edition, and Hospital Level Paediatrics (HLP) guidelines (2017 Edition, Chapter 6 Nephrological/Urological Disorders 2021 update), provide recommendations on diagnosis and empirical antibiotic treatment for UTI in children.[5,6]

The PHC guideline recommends empirical antibiotic treatment for UTI in children when a dipstix test (urine test strip) on a fresh bag specimen is positive for leucocytes and remains positive on a second specimen, or is positive for leucocytes or nitrites with symptoms of UTI, or is positive for both leucocytes and nitrites. The guideline recommends that all children <3 months with any UTI and children >3 months who appear ill should receive intramuscular ceftriaxone and be transferred to hospital.[5] Both PHC and HLP guidelines recommend oral amoxicillin/clavulanic acid (co-amoxiclav) for children >3 months who are unwell but not acutely ill and who are not vomiting. Parenteral treatment is recommended for all neonates and acutely ill infants with either intravenous (IV) co-amoxiclav or cefotaxime. If there is no improvement after 24 hours of treatment, infection with a resistant organism should be suspected and treatment should be according to culture and AST results and a specialist consulted. If there is good clinical response, treatment may be changed to oral co-amoxiclav. Recommended duration of therapy is 3- 7 days but extended to 10-14 days in infants with acute pyelonephritis or septicaemia.[5,6] The HLP guidelines use urine culture based diagnostic criteria, on aseptically collected specimens, if the screening urine dipstix test of a bag specimen reveals the presence of leucocytes, nitrites, or haematuria. Criteria include: any positive

culture from a suprapubic urine specimen; a catheter specimen with $>10^4$ colony forming units (CFU)/milliliter (mL) of a single organism; a mid-stream clean catch specimen with $>10^5$ CFU/mL of a single organism or persistent culture of a single organism with counts as low as 10^4 CFU/mL.[6] Differentiating uncomplicated versus complicated and lower versus upper UTI is controversial and challenging, particularly in infants and young children who present with non-specific symptoms and signs. Treatment recommendations are therefore based on age, severity of presentation, ability to tolerate oral antibiotics and response to initial treatment.[5,6]

Significant and increasing rates of resistance to commonly used first-line antibiotics for treatment of UTI have been described globally and in South Africa.[7-12] A systematic review and meta-analysis of the global prevalence of antibiotic resistance in paediatric UTI caused by *Escherichia coli (E. coli)* in primary care was published in 2016.[8] The data were stratified by whether the country was included in the Organisation for Economic Co-operation and Development (OECD). Thirty-three studies done in OECD countries showed a pooled prevalence of resistance was: 8.2% (95% confidence interval (CI) 7.9-9.6%) for co-amoxiclav, 2.1% (0.8-4.4%) for ciprofloxacin, and 1.3% (0.8-1.7%) for nitrofurantoin. Twenty-five studies done in countries outside the OECD, including lower-income countries, showed resistance was significantly higher: 60.3% (40.9-79.0%) for co-amoxiclav, 26.8% (11.1-43.0%) for ciprofloxacin and 17.0% (9.8-24.2%) for nitrofurantoin. There was evidence that resistant isolates were more common in those with previous exposure to over-the-counter antibiotics available in some lower-income countries[8].

A laboratory-based surveillance study reporting antimicrobial susceptibility patterns of *E. coli* from urine samples from 19 public and private sector laboratories across South Africa between 2007 and 2011 showed decreasing susceptibility to β-lactam and fluoroquinolone antibiotics.[10] Susceptibility to co-amoxiclav declined from 84-81% in private and from 78-75% in public sectors, for cefuroxime from 94-88% in private and 92-88% in public, and ciprofloxacin from 86-81% in private and 80-73% in the public sector. This study did not stratify data by age nor did the study design allow differentiation between community- and hospital-acquired infections. A study conducted at Tygerberg Hospital (tertiary level) in the Western Cape published in 2021 described urine culture and AST results in children <14 years (median age 12.1 months, interquartile range (IQR) 2.9-42.3 months) with suspected UTI admitted between January 2012 and December 2013.[11] Among 282 urine samples that met the study definition of UTI ($>10^5$ CFU/mL growth of a single organism and $>10^3$ leucocytes/mL regardless of urine sample collection methods), 170 (60%) were community-acquired (defined as infection identified on presentation to the paediatric emergency unit in the absence of any prior admission in the preceding 30 days). *E. coli* accounted for 67% of community-acquired infections with *Klebsiella pneumoniae (K. pneumoniae)*, *Proteus mirabilis* and *Enterococcus* species accounting for 10%, 5% and 5% respectively. Analysis of AST showed that among 129/143 (90%) of the *E. coli* isolates tested, 80 (62%) were susceptible to co-amoxiclav, but among 62/64 (97%) of *K. pneumoniae* isolates tested, only 7/62 (11%) were susceptible to co-amoxiclav. In addition, *E. coli* and *K. pneumoniae* accounted for 69/75 (92%) of the total number of ESBL-producing organisms causing UTI, of which 19/75 (25%) were community-acquired infections.

Changing epidemiology should be considered in the development of empirical antibiotic treatment recommendations and antibiotic stewardship programmes. This is especially important among patients with underlying risk factors for severe infections or poor outcomes, and in areas with a

high prevalence of antibiotic resistance in order to minimise treatment failure due to discordant empirical therapy (cultured isolate is non-susceptible to empirical antibiotic selected). This must be balanced with the imperative of preserving antibiotic options for directed therapy of UTIs due to resistant bacterial infections.[13] Recent data on the epidemiology and antibiotic susceptibility profile of community-acquired bacterial UTI in children in Cape Town is lacking.

Aims

The study aims to describe the demographic and clinical profile of patients with community-acquired, culture-confirmed UTI in children at Victoria Hospital, a district hospital in Cape Town, and the aetiology and AST profile of bacteria causing these infections. The study also aims to evaluate the appropriateness of the empirical antibiotic treatment recommendations for UTIs in children in the SA STG/EML in the context of the study results

Methods

This study is a retrospective review of medical records and laboratory results. Urine specimens sent from all children <10 years for routine microscopy, culture and AST to the National Health Laboratory Service (NHLS) microbiology laboratory at Groote Schuur Hospital from Victoria Hospital between 1 February 2016 and 31 July 2019 and who met study criteria for a culture confirmed bacterial UTI were included. This was a convenience sample.

Inclusion criteria

Specimens were included if they met the study definition of a culture-confirmed bacterial UTI, modified from the SA STG/EML HLP guidelines (2017 Edition, Chapter 6 Nephrological/Urological Disorders 2021 update).[6] (1) any culture from a suprapubic aspirate, (2) culture of $>10^4$ CFU/mL of a single organism from a catheter urine specimen, (3) culture of $>10^5$ CFU/mL of a single organism from a mid-stream clean catch specimen or if the urine sampling technique was not indicated in the laboratory or medical records.[6] Community-acquired UTI were included and accepted to be an infection of the urinary tract at presentation or within 48 hours of hospital admission.

Exclusion criteria

Specimens were excluded if they met the study definition of a contaminant which was (1) a urine specimen from a catheter specimen, mid-stream clean catch specimen or if the urine sampling technique was not indicated and the specimen had growth of two or more organisms, or (2) growth of non-uropathogens including *Lactobacillus* species and coagulase-negative staphylococci. If more than one urine specimen from the same participant cultured the same organism within 30 days and met criteria for inclusion into the study, the second specimen was excluded.

Culture and susceptibility testing

After inoculation with calibrated loops on chromogenic media for uropathogens, urine plates were incubated aerobically for 18 - 24 hours at ~35°C. Growth of a single organism (or up to two organisms for suprapubic or in/out catheter urine) was semi-quantified and identified using the VITEK 2 automated system (bioMérieux, Marcy-l'Étoile, France), biochemical or antigen-detection methods. Susceptibility testing was performed using VITEK 2, or disc or gradient

diffusion antibiotic susceptibility testing methods where relevant. Results of antibiotic susceptibility tests were interpreted according to Clinical Laboratory and Standards Institute M100 guidelines for that current year. In this study, antibiotic susceptibility was classified as either susceptible or non-susceptible, with the non-susceptible category including both the 'intermediate' and 'resistant' categories.

Data collection and analysis

Urine microscopy and culture results of children <10 years of age were extracted from the NHLS laboratory information system. Culture and AST results meeting study criteria were entered into a study database. Medical records, where available, were reviewed, and demographic, clinical and antibiotic management data were captured in the database.

Descriptive analyses were performed using Stata v 14.2 (Stata Corp, College Station, TX) and Microsoft Excel. Categorical variables were described using absolute values and percentages; continuous variables were described using mean and standard deviation for normally distributed data, and median and interquartile range for non-normally distributed data.

Ethical approval was obtained from Human Research Ethics Committee of the University of Cape Town (HREC ref: 413/2019). The study was conducted according to the principles of the Declaration of Helsinki. As this was a retrospective review of medical records and laboratory results, the study received a waiver to obtain informed consent from study participants' parents or legal guardians.

Results

Between 1 February 2016 and 31 July 2019, 528 urine specimens from children <10 years of age who attended Victoria Hospital were submitted to the NHLS for microscopy, culture and AST. Eighty-nine of these specimens met criteria for inclusion into the study (Figure 1). Medical records were available for 78/89 (88%) participants.

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Demographic and clinical characteristics

The median age of participants was 25 months (IQR 0-117 months) and 72% (56/78) were <5 years of age, and 58% (45/78) were female. The weight-for-age Z score was between -2 and +2 standard deviations in 81% (63/78) participants. One participant had known chronic renal disease. There were 2 participants living with HIV, 1 was on antiretroviral therapy (ART) with a suppressed viral load and the other one was not on ART. A previous UTI was documented in 5% (4/76) but clinical and laboratory details regarding the previous UTI episodes, including organisms cultured, AST results and antibiotics received, were unavailable.

One or more non-specific systemic features of UTI listed in the STG/ EML SA HLP guidelines were documented in 65% (51/78) participants with the most common features being temperature instability in 76% (39/51), poor feeding in 47 % (24//51) and diarrhoea in 31% (16/51). At least one urinary symptom was documented in 51% (40/78) participants with the most common being dysuria in 58% (23/40), abdominal pain in 45% (18/40) and frequency in 23% (9/40). Admission to hospital was required in 42% (33/78) participants.

Sixty -eight percent (53/78) urine specimens were collected in the hospital emergency centre, none were collected after 48 hours of admission to hospital and none of the participants were residents of a long-term healthcare facility. Only 33% (26/78) participants had documentation of the urine sampling technique, 69% (18/26) were collected via in/out catheterisation and 15% (4/26) each from a urine bag or as a clean-catch specimen, and none were recorded as being collected from an indwelling urinary catheter or suprapubic aspirate. Fifteen participants of 78 (19%) had blood cultures taken of which 27% (4/15) yielded a positive culture result, all *E. coli*. Serum urea and creatinine was tested in 40% (31/78) participants with evidence of renal impairment in 16% (5/31) of those tested. Ultrasound of the kidneys, ureters, and bladder was done in 67% (51/76) participants, results were available for 90% (46/51)) and were abnormal in 12% (6/51) but the specific urinary tract abnormality was not documented in the medical records.

Laboratory results

The majority of participants had leucocytes on urine microscopy (90% (80/89)), with 71% (63/89) having >10 leucocytes/mm^3. Erythrocytes were less frequently seen on microscopy (29% (26/89)). Six participants had either epithelial cells or excess debris seen on microscopy suggesting potential contamination during specimen collection.

There were 89 isolates from 89 samples. Enterobacterales accounted for 88 (99%) of the organisms cultured: 85% were *E. coli,* 4% *K. pneumoniae*, 3% *K. oxytoca*, 3% *Proteus mirabilis* and 2% *Enterobacter cloacae*. Table 1 shows AST data for the Enterobacterales. *Enterococcus* species was isolated from a single specimen and AST results were not available

Eleven isolates (4 *E. coli*, 5 *Klebsiella* and 2 *Enterobacter cloacae*) were ESBL producers. Medical records were available for 10 participants with ESBL-producing organisms and were reviewed for specific risk factors for ESBL infection. Six were <1 year of age, 2 were born prematurely, and none were residents of long-term healthcare facilities. Previous antibiotic exposure was not clearly documented in this group although 2 had been exposed to antibiotics prior to the urine specimen being taken during the current episode of illness. None had recent surgery, 3 were documented as having an underlying neurological condition and 1 had chronic haematological disease. None had an indwelling urinary catheter or medical device in-situ, documented previous UTI or chronic renal disease. Information on prior hospital admission was unavailable. In terms of disease severity, 50% of this group were admitted to hospital, 1 cultured *E. coli* on blood culture and 1 had an abnormal renal function test. None of those who had an ultrasound of the kidneys, ureters, and bladder performed had any anatomical abnormalities detected. Seven (64%) of these ESBL producers had a piperacillin/tazobactam minimum inhibitory concentration (MIC) ≤ 16 ug/mL. Susceptibility to amikacin was present in 6 (55%) isolates, gentamicin in 3 (27%), ciprofloxacin in 8 (73%), nitrofurantoin in 7 (64%) and trimethoprim/sulfamethoxazole in 2 (18%).

Seventy-four participants (95%) were started on empirical antibiotics, with an oral antibiotic prescribed in 54 (73%) and an intravenous antibiotic in the remainder (Table 2). Ciprofloxacin and ceftriaxone were respectively the commonest oral and parenteral antibiotics prescribed. The initial empirical antibiotic selected aligned with SA STG/EML recommendations in 32 (43%) participants and in 48 (65%) participants the cultured isolate was susceptible to the empirical antibiotic regimen selected.

Table 1. Antibiotic susceptibility of Enterobacterales isolated

	Enterobacterales (N= 88) n (%)	***E. coli* N= 76 n (%)**	***K. pneumoniae* N= 4 n (%)**	***K. oxytoca* N= 3 n (%)**	***P. mirabilis* N= 3 n (%)**	***E. cloacae* complex N= 2 n (%)**
Ampicillin/ Amoxicillin	13 (15)	11 (14)	0 (0)	0 (0)	2 (67)	Not tested
Amoxicillin/ clavulanic acid	51 (58)	46 (61)	1 (25)	1 (33)	3 (100)	0 (0)
Cefuroxime (oral)	74 (84)	69 (91)	1 (25)	1 (33)	3 (100)	0 (0)
Ceftriaxone/ Cefotaxime	77 (88)	72 (95)	1 (25)	1 (33)	3 (100)	0 (0)
Ceftazidime	77 (88)	72 (95)	1 (25)	1 (33)	3 (100)	0 (0)
Cefepime	77 (88)	72 (95)	1 (25)	1 (33)	3 (100)	0 (0)
Piperacillin/ tazobactam	70 (80)	61 (80)	3 (75)	2 (67)	3 (100)	1 (50)
Ertapenem	88 (100)	76 (100)	4 (100)	3 (100)	3 (100)	2 (100)
Imipenem	85 (97)	76 (100)	4 (100)	3 (100)	0 (0)	2 (100)
Meropenem	88 (100)	76 (100)	4 (100)	3 (100)	3 (100)	2 (100)
Ciprofloxacin	83 (94)	74 (97)	3 (75)	3 (100)	3 (100)	0 (0)
Gentamicin	76 (86)	71 (93)	1 (25)	1 (33)	3 (100)	0 (0)
Amikacin	86 (98)	76 (100)	4 (100)	2 (67)	3 (100)	1 (50)
Nitrofurantoin	79 (90)	74 (97)	1 (25)	3 (100)	Not tested	1 (50)
Trimethoprim/ sulfamethoxazole	33 (38)	28 (37)	1 (25)	1 (33)	2 (67)	1 (50)

E. coli, *Escherichia coli*; *K. pneumoniae*, *Klebsiella pneumoniae*; *K. oxytoca*, *Klebsiella oxytoca*; *P. mirabilis*, *Proteus mirabilis*; *E. cloacae* complex, *Enterobacter cloacae* complex

Table 2. Initial empirical antibiotic treatment of study participants (N=78).

Empirical antibiotic	**n (%)**
Oral	
Ciprofloxacin	24 (31)
Amoxicillin/clavulanic acid	21 (27)
Amoxicillin	2 (3)
Trimethoprim/sulfamethoxazole	2 (3)
Azithromycin	2 (3)
Penicillin VK	2 (3)
Cefalexin	1 (1)
Parenteral	
Ceftriaxone	12 (15)
Ceftriaxone + ampicillin	2 (3)
Cefotaxime + ampicillin	2 (3)
Gentamicin	2 (3)
Ampicillin + gentamicin	1 (1)
Meropenem	1 (1)
No antibiotic started prior to urine culture result	4 (5)
Initial empiric antibiotic selected aligns with SA STG/EML recommendations, (N=73)	32 (43)

SA STG/EML, South African Standard Treatment Guidelines / Essential Medicines List

Discussion

This study described children with culture-confirmed UTI presenting to a district hospital in Cape Town between 1 February 2016 and 31 July 2019. Enterobacterales accounted for the majority (99%) of cultured isolates with a predominance of *E. coli* (86%). Only 58% of Enterobacterales and specifically 61% of *E. coli* isolates were susceptible to co-amoxiclav, the first-line empirical antibiotic for UTI treatment recommended in the SA STG/EML; however, 88% of Enterobacterales and 95% of *E. coli* isolates were susceptible to cefotaxime/ceftriaxone, the alternative first-line empirical antibiotic recommended for neonates and acutely ill infants. The number of *Klebsiella* species (7), *Proteus mirabilis* (3) and *Enterobacter cloacae* (2) isolated was too small to draw any significant interpretation regarding AST for these organisms. Extended spectrum β-lactamase-producing organisms accounted for 12% of the isolates cultured in these children with community-acquired UTI and there were no carbapenem-resistant isolates. The single non-Enterobacterales organism was identified as *Enterococcus* species, but AST was not performed as per the laboratory's standard operating procedure. Although not directly comparable to our study in design or population, recent studies support our findings that only approximately 55-65% of *E. coli* isolates, the commonest uropathogen causing community-acquired UTI in children, are susceptible to co-amoxiclav.[10-12]

Other oral antibiotics to which the Enterobacterales isolated in our study showed relatively high rates of susceptibility include ciprofloxacin (94%), nitrofurantoin (90%) and cefuroxime (84%) and could therefore be considered for empirical therapy for children with UTI. Nitrofurantoin is currently only available as 50 mg or 100 mg tablets in SA and the recommended dose for children is approximately 1.5 mg/kg/dose 6 hourly making dosing impractical for many young children. Nitrofurantoin was used in a prospective study of 50 children (mean age 7.5 years) with acute cystitis due to ESBL-producing *E. coli* susceptible to nitrofurantoin who were treated for 10 days. Urine culture was sterile in 98% of patients after treatment and renal scintigraphy performed during the UTI episode and 1-3 months later demonstrated non-scarring in 96% of patients.[14]. Notably, nitrofurantoin is not recommended for the treatment of pyelonephritis.[15] Ciprofloxacin has the advantages of more practical twice daily dosing and availability of an oral suspension. However, longer-term complications including arthropathy and cardiovascular effects are concerning, and it should be used with caution and when suitable alternatives are unavailable.[16] Cefuroxime is also dosed twice daily and available in an oral suspension formulation. Although ESBL-producing Enterobacterales are resistant to cefuroxime and other cephalosporins, these organisms only accounted for 12% of the isolates in this study and cefuroxime could be considered as a first-line empiric antibiotic option for community-acquired UTI in children.

Ninety-five percent of children in this study were started on empirical antibiotic treatment, the majority (73%) oral, with only 27% starting oral co-amoxiclav. Ciprofloxacin and ceftriaxone respectively were the commonest oral and parenteral antibiotics prescribed. A wide array of antibiotics was selected for initial therapy, suggesting participants may have had concurrent infections. The high rate of hospital admission (42%) suggests that participants were systemically unwell. Intravenous co-amoxiclav, recommended in the SA STG/EML as an option for neonates and acutely ill infants with UTI, was not prescribed. This may reflect the need to provide systemic antibiotics for suspected or confirmed meningitis with ceftriaxone or cefotaxime, or lack of availability of IV co-amoxiclav during the study period. From the medical record review, it was

not possible to differentiate those who had antibiotics started to specifically target UTI versus those starting antibiotics for a suspected infection other than or in addition to a UTI. As a result, compliance with the SA STG/EML guidelines on recommended empirical antibiotic treatment for UTI was low (43%) but in 65% of participants started on empirical treatment the organism subsequently isolated from urine was susceptible. Although the selection of empirical antibiotics may not always have been directed at a UTI, our data suggest a prescriber tendency to use alternatives to co-amoxiclav, particularly oral ciprofloxacin. This could reflect prescriber concerns regarding the side-effect profile (particularly antibiotic-associated diarrhoea[17]) and dosing complexity of oral liquid formulations of co-amoxiclav for young children, the low level of prescriber adherence to the SA STG/EML treatment recommendations could reflect a lack of familiarity with these guidelines, or a perception that the recommendations are inappropriate in relation to current antibiotic susceptibility profile of organisms causing UTI. A 2018 study investigating antibiotic prescribing practice and adherence to guidelines in primary care in Cape Town showed that despite the availability of published national guidelines, adherence to these was low with an overall adherence rate of 4.5% and the system with the poorest adherence to guidelines was the urological system.[17] Similar poor adherence to guidelines has been shown in international studies with low levels of adherence (14-29%) to antibiotic selection and therapy duration in the treatment of UTI.[18]

One of the strengths of this study is that it incorporated the definition of a culture-confirmed UTI according to the SA HLP STG/EML[6] modified to include culture criteria for urine specimens for which the sampling technique was unknown. The stringent microbiological criteria with semi-quantitative CFU cut-off values reduce the likelihood of including culture results that reflect contamination due to poor urine sampling techniques rather than true infection. The American Academy of Pediatrics reports that up to 88% of positive culture results obtained by using a urine bag specimen can be false positive [19] and in comparison with suprapubic aspirates, the sensitivity of clean-catch urine specimens for diagnosis has been calculated to range from 75-100% and the specificity from 57-100%.[2,20] In our study, only 33% of participants had documentation of the urine sampling technique in the medical records. In 69% of these, in/out catheterisation was performed, and in 15% each it was obtained from a urine bag or a clean-catch specimen. None were recorded as being from an indwelling urinary catheter or suprapubic aspirate.

The SA HLP STG/EML UTI definition includes a urine dipstix result showing positive leucocyte esterase activity, nitrites and haematuria as a clinical diagnostic criterion, however urine microscopy results are not included in the SA HLP STG/EML as diagnostic criteria.[6] The absence of leucocytes or presence of epithelial cells from a positive culture may signify contamination of the urine specimen by skin or gastrointestinal flora because of poor urine sampling technique. In our study, urine dipstix results were poorly documented in the medical records and could not be included but urine microscopy showed that 90% of specimens had leucocytes of which 79% had >10 leucocytes/mm^3 (numerous) seen supporting that these were potentially true UTIs. There were 6/89 (7%) specimens that had either epithelial cells or excess debris seen on microscopy suggesting potential contamination during specimen collection in only a few participants.

This study has several limitations. It was based at a district level public sector hospital in Cape Town and the results may not be generalisable to children in other settings. In particular, the participants in this study had what were assessed as community-acquired infections. The study

design was a retrospective review of medical and laboratory records, and there was limited data on prior UTI episodes or antibiotic exposures at other healthcare facilities. The specific clinical indication for submitting a urine specimen to the laboratory could not be easily determined, and the urine sampling technique and indication for empirical antibiotics was poorly documented. The stringent study definition of a UTI and the poor documentation of urine sampling technique in the medical records resulted in the exclusion of many specimens with pure growth of a uropathogen but with a semi-quantitative count that did not fulfill the study definition of a UTI. Data pertaining to adjustments made to antibiotic treatment and clinical and microbiological outcomes were not collected in this study. Some participants may have shown a favourable clinical response despite treatment with antibiotics to which the organism isolated was non-susceptible, others may have required the use of an alternative antibiotic, some may have developed persistent or recurrent UTI. Future research is required to compare antibiotic susceptibility patterns among children with community and healthcare-associated UTI, especially those with resistant uropathogens, and to describe the outcome of treatment with different antibiotic regimens.

Conclusions

Community-acquired UTI in children under 10 years of age at this district level hospital was almost entirely caused by *Enterobacterales* with a predominance of *E. coli*. The study showed a low rate of susceptibility to co-amoxiclav, the currently recommended oral antibiotic in South African treatment guidelines. This data should be taken into consideration in updating clinical guidelines on empirical antibiotic therapy in children with UTI.

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Author contributions. All authors contributed to the study designs, critical review of the manuscript; and read and approved the final manuscript.

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Conflicts of interest. None.

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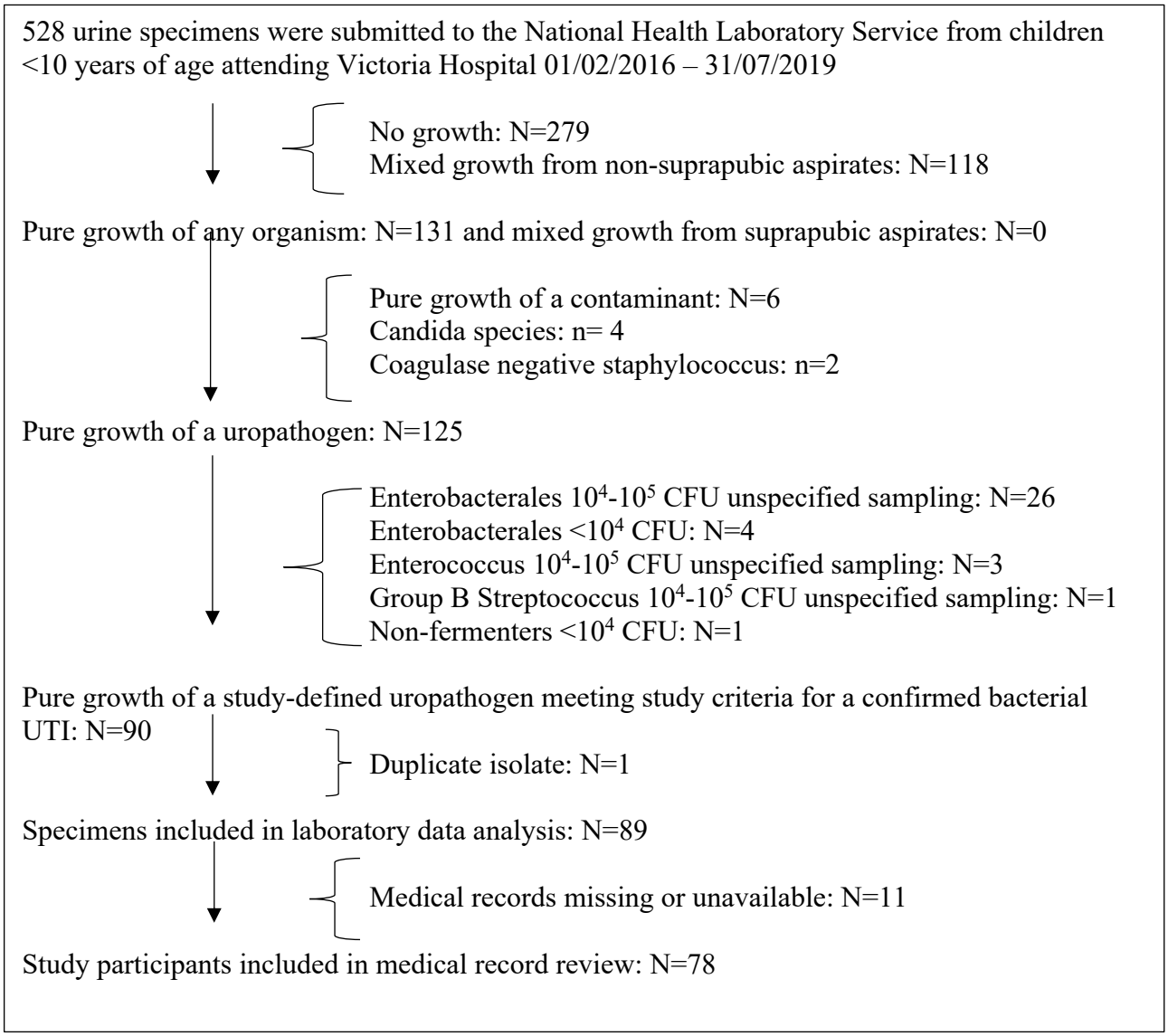

CFU, colony forming units; UTI, urinary tract infection

Figure 1. Selection of urinary tract infection episodes for analysis

My First Instrument

Study number	_____
Folder number	_____
Date of birth	_____
Date of urine sample	_____
Gender	◯ male ◯ female ◯ unknown
Source of patient	◯ inpatient ◯ out patient ◯ unknown
Source of outpatient	◯ casualty ◯ POPD ◯ unknown
Source of inpatient	◯ POPD ◯ Casualty ◯ Private ◯ False Bay Hospital ◯ Red Cross Hospital ◯ Unknown
Admission to long term health facility	◯ Yes ◯ No ◯ Unknown
Name of facility	_____
Date of admission to health facility	_____
Born in hospital	◯ yes ◯ no ◯ unknown
Name of hospital	_____
Date of discharge from hospital	_____
weight	_____

height	_____
nutritional oedema	◯ yes ◯ no ◯ unknown
HIV exposure	◯ exposed ◯ unexposed ◯ unknown
HIV status	◯ positive ◯ negative ◯ unknown
ARV's	◯ on treatment ◯ not on treatment ◯ unknown
bactrim prophylaxis	◯ yes ◯ no ◯ unknown
virological suppression	◯ suppressed ◯ unsuppressed ◯ unknown
Clinical presentation: systemic	☐ temperature instability ☐ poor feeding ☐ irritability ☐ failure to thrive ☐ jaundice ☐ vomiting ☐ diarrhoea ☐ seizures ☐ other
clinical presentation: renal	☐ frequency ☐ enuresis ☐ dysuria ☐ loin pain ☐ lower abdominal pain ☐ bed wetting ☐ other
UTI diagnosis made	◯ upper tract ◯ lower tract ◯ unspecified

other diagnosis	☐ neonatal sepsis ☐ sepsis outside neonatal period ☐ meninigitis ☐ diarrhoea ☐ malnutrition ☐ pneumonia ☐ bronchiolitis ☐ TB ☐ URTI ☐ appendicitis ☐ febrile convulsions ☐ other ☐ none ☐ unknown
Chronic illness	☐ constipation ☐ ex premature ☐ atopic ☐ haematological ☐ neurological ☐ pulmonary ☐ upper airway ☐ hepatic ☐ cardiac ☐ renal ☐ post operative ☐ unknown ☐ none
previous UTI	◯ yes ◯ no ◯ unknown
Date of previous UTI	_____
organism in past UTI	_____
how urine specimen taken	◯ urine bag ◯ in- out catheter ◯ SPA ◯ in dwelling catheter ◯ clean catch ◯ unspecified
area specimen sent from	◯ casualty ◯ POPD ◯ Paediatric ward ◯ other facility ◯ unknown
antibiotic received prior to urine sample being sent	◯ yes ◯ no ◯ unknown
empiric antibiotic	_____

definitive antibiotic	_____
antibiotic stewardship chart used	◯ yes ◯ no ◯ unknown
antibiotic stewardship chart completed	◯ yes ◯ no ◯ unknown
Imaging done	◯ yes ◯ no ◯ unknown
imaging normal	◯ normal ◯ abnormal ◯ unknown result

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

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25 June 2019

HREC REF: 413/2019

Dr J Nuttall
Department of Paediatrics and Child Health
5th Floor, Institute of Child Health Building
Red Cross War Memorial Children's Hospital
Rondebosch

Dear Dr Nuttall

PROJECT TITLE: URINARY TRACT INFECTION IN CHILDREN AT VICTORIA HOSPITAL, A DISTRICT HOSPITAL IN CAPE TOWN, SOUTH AFRICA. (MMED CANDIDATE: DR D SHEPHERD)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 June 2020.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

We acknowledge that the student: Dr D Shepherd will also be involved in this study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.

Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

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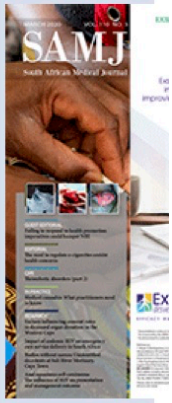

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- Please be sure to insert proper symbols e.g. µ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
- If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

SAMJ is a generalist medical journal, therefore for articles covering genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.

- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

**NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'

- Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Preparation notes by article type

- Research
- Editorials
- CME
- In Practice and Case reports
- Reviews
- Clinical trials
- Correspondence
- Obituaries
- Book reviews
- Guidelines

Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text .

Structured abstract

- This should be 250-400 words, with the following recommended headings:
  - **Background:** why the study is being done and how it relates to other published work.
  - **Objectives:** what the study intends to find out
  - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
  - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
  - **Conclusion:** must be supported by the data, include recommendations for further study/actions.
- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Here is an example of a good abstract.

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc)that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after

studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

Editorials

Guideline word limit: 1 000 words

These opinion or comment articles are usually commissioned but we are happy to consider and peer review unsolicited editorials. Editorials should be accessible and interesting to readers without specialist knowledge of the subject under discussion and should have an element of topicality (why is a comment on this issue relevant now?) There should be a clear message to the piece, supported by evidence.

Please make clear the type of evidence that supports each key statement, e.g.:

- expert opinion
- personal clinical experience
- observational studies
- trials
- systematic reviews.

CME (by invite only)

CME is intended to provide readers with practical, up-to-date information on medical and related matters. It is aimed at those who are not specialists in the field.

From January 2016, all CME articles will be printed in full in the *SAMJ*. Please try to adhere strictly to the guidelines on word count as we have a page limit for the print issue of the *SAMJ*. We reserve the right to place some tables and reference lists online if this is necessary for space.

In practice, this means that each CME topic usually covers two issues of the print issue of the *SAMJ*.

The guest editor, in consultation with the editor, is responsible for convening a team of authors, deciding on the subjects to be covered and for reviewing the

manuscripts submitted. The suggestion is for 4 - 5 articles, although there is some room for flexibility contingent on discussions with the editor.

For queries about these guidelines please feel free to contact the CME editor, Dr Bridget Farham, by email (ugqirha@iafrica.com) or telephone (+27 (0)82 452 2860)

Review process

The guest editor reviews the articles and returns them to the CME editor for review and final approval.

Guest editorials

Guideline word limit: 1 000 words

- Include the guest editor's personal details (qualifications, positions, affiliation, e-mail address, and a short personal profile (50words)).
- If possible, include a photograph of the author(s) at high enough resolution for print. It is preferable to provide two guest editorials, one for each issue, so that the content of the articles in each issue is covered.

Articles

Guideline word limit: 2 000 - 3 000 words

- Each article requires an abstract of ±200 words.
- The editor reserves the right to shorten articles but will send a substantially shortened article back for author approval.

Personal details

Please supply: Your qualifications, position and affiliations and MP number (used for CPD points); Address, telephone number and fax number, and your e-mail address; and a short personal profile (50words)and a few words about your current fields of interest.

In Practice

Guideline word limit: 2 000 - 3 000words

This section includes articles that would previously have been accepted into the Forum section, and case reports.

In practice articles are those that draw attention to specific issues of clinical, economic or political interest regarding medicine and healthcare in southern Africa. They are assigned to a topic:

- Case report
- Clinical practice
- Clinical alert
- Issues in medicine
- Issues in public health
- Healthcare delivery
- Medicine and the environment
- Medicine and the law
- Cochrane corner

An In Practice article should follow the following format – sub-headings are not necessary, but may be used for clarity:

- Author affiliations and qualifications: to be the same as for Research. Provide all authors' names and initials, qualifications and full affiliations, and corresponding author.
- Short abstract: does not need to be structured, but should capture the essential features of the article
- Introduction: the reason for the article and the issue being addressed
- Recent research, discussion, local policy around the issue – include your own research where appropriate
- All statements should be referenced and, if opinion only, this should be stated
- Discussion: how this article adds to the discussion around a particular topic

- If a clinical practice or policy point is at issue, this needs to be emphasised, using a box with highlights if appropriate.

Essentially In practice is an opportunity for a more discursive approach to topics of clinical, economic or political importance in southern African health systems. It is not an opportunity to put forward unsubstantiated opinions!

Case reports

The *SAMJ* has recently started to accept case reports. The cases must come from Africa, preferably southern Africa unless the condition is common to all African countries, and must be either a completely new description of a clinical condition or result (use Google!) or a case that highlights important practice or management issues.

Please use the following format for case reports:

- Title of case: do not include the words 'a case report' in the title
- Summary/abstract: up to 150 words summarising the case presentation and outcome
- Background: why is this case important and why did you write it up?
- Case presentation: presenting features, medical, social, family history as appropriate
- Case management: should be according to best practice, and if not, please explain why
- Investigations, if relevant: save space by simply saying 'normal' if, for example, renal function was completely normal, rather than listing normal results, highlight the abnormal – or indeed the normal if this is clinically significant
- Differential diagnosis, if relevant
- Treatment, if relevant
- Outcome and follow-up
- Discussion – a VERY BRIEF review of similar published cases
- Teaching points: 3 - 5 bullet points
- References: as per the *SAMJ* house style
- Tables and figures: keep to a minimum. Use clinical images where relevant – we need hi-res versions for print, and identifiable persons must have a consent form
- Patient consent: please include a statement about patient consent to a written case report. This should be uploaded as a supplementary file.

Clinical trials

Guideline word limit: 4000 words

As per the recommendations published by the International Committee of Medical Journal Editors (ICMJE), clinical trial research is any research that assigns individuals to an intervention, with or without a concurrent comparison/control group to study the cause-and-effect relationship between the intervention and health outcomes. All clinical trials should be registered with the appropriate national clinical trial registry (or any international primary register, if relevant), and the trial registration number should be cited at the end of the abstract. Since 1st December 2005, all clinical trials conducted in South Africa have been required to be registered in the South African National Clinical Trials Register. The *SAMJ* therefore requires that clinical trials be registered in the relevant public trials registry at or before the time of first patient enrollment as a condition for publication. The trial registry name and registration number must be included in the manuscript.

Please refer to the general guidelines for all papers at the top of this article for additional requirements with respect to ethics approval, funding, author contributions, etc. The format of original research articles should be followed for reporting of clinical trial results.

Review articles

Guideline word limit: 4 000 words

These are welcome, but should be either commissioned or discussed with the

Editor before submission. A review article should provide a clear, up-to-date account of the topic and be aimed at non-specialist hospital doctors and general practitioners.

Please ensure that your article includes:

- Abstract: unstructured, of about 100-150 words, explaining the review and why it is important
- Methods: Outline the sources and selection methods, including search strategy and keywords used for identifying references from online bibliographic databases. Discuss the quality of evidence.
- When writing: clarify the evidence you used for key statements and the strength of the evidence. Do not present statements or opinions without such evidence, or if you have to, say that there is little or no evidence and that this is opinion. Avoid specialist jargon and abbreviations, and provide advice specific to southern Africa.
- Personal details: Please supply your qualifications, position and affiliations and MP number (used for CPD points); address, telephone number and fax number, and your e-mail address; and a short personal profile (50 words) and a few words about your current fields of interest.

Correspondence (Letters to the Editor)

Guideline word limit: 500 words

Letters to the editor should relate either to a paper or article published by the SAMJ or to a topical issue of particular relevance to the journal's readership

- May include only one illustration or table
- Must include a correspondence address.

Book reviews

Guideline word limit: 400 words

Should be about 400 words and must be accompanied by the publication details of the book. Provide a hi-res image of the cover if possible (with permission from the copyright holder).

Obituaries

Guideline word limit: 400 words

Should be offered within the first year of the practitioner's death, and may be accompanied by a photograph.

Guidelines

Guidelines should always be discussed with the Editor prior to submission.

Because of the intensive review process required to ensure Guidelines are independent, evidence-based and free from commercial bias, they are usually published as a supplement to the *SAMJ*, the costs of which must be covered by sponsorship, advertising or payment by the guideline authors/association. We will provide a quote based on the expected length of the guideline and whether it is to appear online only, or in print, which must be accepted by the body putting the guidelines together before submitting the work to the SAMJ.

The Editor reserves the right to determine the scheduling of supplements. Understandably, a delay in publication must be anticipated dependent upon editorial workflow.

All guidelines should include a clear, transparent statement about all sources of funding and an explicit, clear statement of conflicts of interest of any of the participants in the guidelines about industry funding for lectures, research, conference participation etc.

All guidelines should be structured according to Agree II.

Please access this website before putting the guidelines together, download the Agree 11 instrument and use this to put the guidelines together.

All submitted guidelines will be sent to the local Agree II appraisal committee for review and must be endorsed by an appropriate body prior to consideration

and all conflicts of interest expressed.

A structured abstract not exceeding 400 words (recommended sub-headings: *Background, Recommendations, Conclusion*) is required. Sections and sub-sections must be numbered consecutively (e.g. 1. Introduction; 1.1 Definitions; 2.etc.) and summarised in a Table of Contents.

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF or jpeg form.
- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) and refer to consecutively in the text.
- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings, and include units where necessary.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make 'new rows':

Rather:
Each row of data must have its own proper row:

Do not: use separate columns for *n* and %:

Rather:
Combine into one column, *n* (%):

Do not: have overlapping categories, e.g.:

Rather:
Use <> symbols or numbers that don't overlap:

References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. Reference lists must be generated manually and not with the use of reference manager software. Endnotes must* ***not*** *be used.*

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
    - On the Crossref homepage, paste the article title into the 'Metadata search' box.
    - Look for the correct, matching article in the list of results.
    - Click Actions > Cite
    - Alongside 'url =' copy the URL between { }.
    - Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

Some examples:

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. http://dx.doi.org/10.1000/hgjr.182
- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
- Legal references

- Government Gazettes:

National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.

In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.

- Provincial Gazettes:

Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.

- Acts:

South Africa. National Health Act No. 61 of 2003.

- Regulations to an Act:

South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

- Bills:

South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.

- Green/white papers:

South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

- Case law:

Rex v Jopp and Another 1949 (4) SA 11 (N)

Rex v Jopp and Another: Name of the parties concerned

1949: Date of decision (or when the case was heard)

(4): Volume number

SA: SA Law Reports

11: Page or section number

(N): In this case Natal - where the case was heard. Similarly, (C) woud indicate Cape, (G) Gauteng, and so on.

NOTE: no . after the v

- *Other references (e.g. reports) should follow the same format:* Author(s). Title. Publisher place: Publisher name, year; pages.
- Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.
- Unpublished observations and personal communications in the text must **not** appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

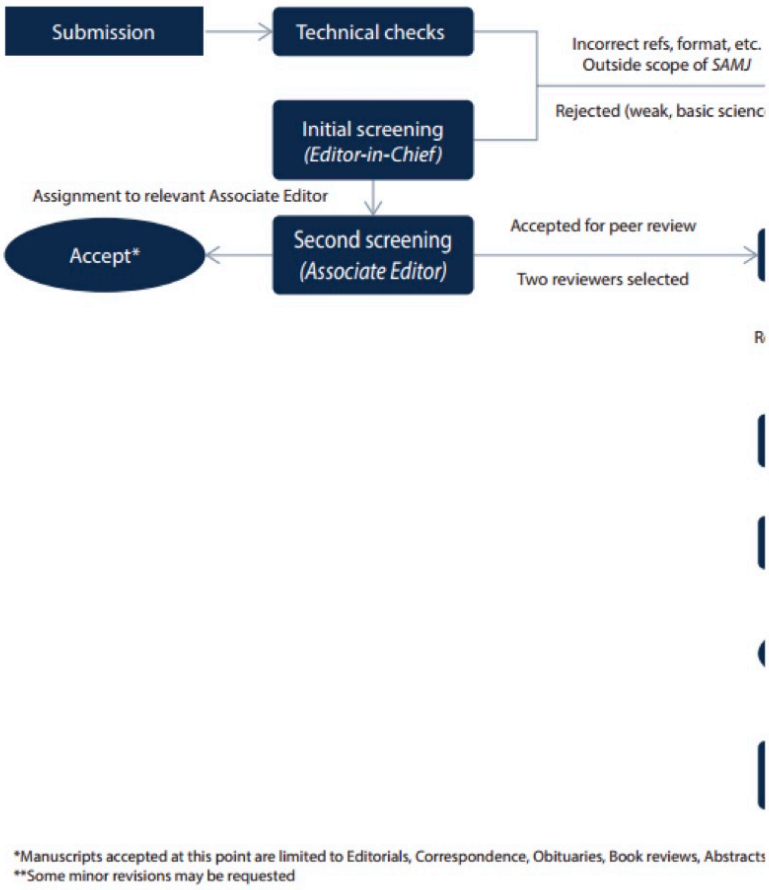
From submission to acceptance

Submission and peer-review

To submit an article:

- Please ensure that you have prepared your manuscript in line with the SAMJ requirements.
- All submissions should be submitted via Editorial Manager
- The following are required for your submission to be complete:
  - Anonymous manuscript (unless otherwise stated)
  - Manuscript
  - Any supplementary files: figures, datasets, patient consent form, permissions for published images, etc.
- Once the submission has been successfully processed on Editorial Manager, it will undergo a technical check by the Editorial Office before it will be assigned to an editor who will handle the review process. If the author guidelines have not been appropriately followed, the manuscript may be sent back to the author for correcting.

Peer-review process



Production process

Please note that there is a 6-month waiting time for publication, once an article has been sent to the production team.

The following process will follow:

1. An accepted manuscript is passed to a Managing Editor to assign to a copyeditor (CE).
2. The CE copyedits in Word, working on house style, format, spelling/grammar/punctuation, sense and consistency, and preparation for typesetting.
3. If the CE has an author queries, he/she will contact the corresponding author and send them the copyedited Word doc, asking them to solve the queries by means of track changes or comment boxes.
4. The authors are typically asked to respond within 1-3 days. Any comments/changes must be clearly indicated e.g. by means of track changes. Do not work in the original manuscript - work in the copyedited file sent to you and make your changes clear.
5. The CE will finalise the article and then it will be typeset.
6. Once typeset, the CE will send a PDF of the file to the authors to complete their final check, while simultaneously sending to the 2nd-eye proofreader.
7. The authors are typically asked to complete their final check and sign-off within 1-2 days. No major additional changes can be accommodated at this point.
8. The CE implements the authors' and proofreader's mark-ups, finalises the file, and prepares it for the upcoming issue.

Changing contact details or authorship

Please notify the Editorial Department of any contact detail changes, including email, to facilitate communication.

Publication

Online v. print

The *SAMJ* is an online journal. The online version of the journal is the one that has the widest circulation, is indexed by bibliographic databases including PubMed and SciELO, and is accessible in academic libraries. A printed edition , containing material selected by the Editor is also published each month and distributed to the membership of the South African Medical Association.

Online

- The full text of all accepted articles is published in full online, open access.
- Citation information of each article is based on its online publication.
- You may want to make use of the advantages of online publication e.g. specify web links to other sources, images, data or even a short video.

Print

- Not all articles will be selected for print.
- An article may be selected for print in a different month from that in which it was published online.
- Research articles will appear *in abstract form only*, if selected for a print edition.

Errata and retractions

Errata

Should you become aware of an error or inaccuracy in yours or someone else's contribution after it has been published, please inform us as soon as possible via an email to publishing@hmpg.co.za,including the following details:

- Journal, volume and issue in which published
- Article title and authors
- Description of error and details of where it appears in the published article
- Full detail of proposed correction and rationale

We will investigate the issue and provide feedback. If appropriate, we will correct the web version immediately, and will publish anerratum in the next issue. The correction will be indexed, as PubMed has a function for linking errata back to the original article. All investigations will be conducted in accordance with guidelines provided by the Committee on Publication Ethics (COPE).

Retractions

Retraction of an article is the prerogative of either the original authors or the editorial team of SAMA. Should you wish to withdraw your article before publication, we need a signed statement from all the authors.

Should you wish to retract your published article, all authors have to agree in writing before publication of the retraction.

Send an email to publishing@hmpg.co.za, including the following details:

- Journal, volume and issue to which article was submitted/in which article was published
- Article title and authors
- Description of reason for withdrawal/retraction.

We will make a decision on a case-by-case basis upon review by the editorial committee in line with international best practices. Comprehensive feedback will be communicated with the authors with regard to the process. In case where there is any suspected fraud or professional misconduct, we will follow due

process as recommended by the Committee on Publication Ethics (COPE), and in liaison with any relevant institutions.

When a retraction is published, it will be linked to the original article.

Indexing

The *SAMJ* has an impact factor of 1.5.

Published articles are covered by the following major indexing services. As such articles published in the *SAMJ* are immediately available to all users of these databases, guaranteed a global and African audience:

- Index Medicus (Medline/PubMed)
- ExcerptaMedica (EMBASE)
- Biological Abstracts (BIOSIS)
- Science Citation Index (SciSearch)
- Current Contents/Clinical Medicine
- Scopus
- AIM
- AJOL
- Crossref
- Sabinet
- Scielo

Sponsored supplements

Contact claudian@samedical.org for information on submitting ad hoc/commissioned supplements, including guidelines, conference/congress abstracts, Festschrifts, etc.

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Material submitted for publication in the *SAMJ* is accepted provided it has not been published or submitted for publication elsewhere. Please inform the editorial team if the main findings of your paper have been presented at a conference and published in abstract form, to avoid copyright infringement.

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