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Telephone: + 94 11 2695300 Ext 315 and
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Fax: + 94 11 447118
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Cover Picture

Louis Herbert, First Canadian Apothecary (1605, A.D)

Parisian apothecary Louis Herbert in 1605 helped Champlain establish Canada's first settlement at Port Royal (Nova Scotia); cared for its sick, and cultivated drug plants. Later, at Quebec, he established the first farm in Canada.

The Sri Lanka Prescriber

Management of urinary tract infection (UTI) in adults

Key points

- Send urine cultures in complicated UTIs or infections extending beyond lower urinary tract, prior to starting empirical antibiotics and change antibiotics accordingly after the culture results.
- Use narrow-spectrum antibiotics for uncomplicated lower urinary tract infections.
- Avoid multiple antibiotics for UTI in the absence of sepsis and low suspicion of drug-resistant causative organisms.
- Amoxicillin is not recommended due to poor efficacy and high antibiotic resistance worldwide.
- Avoid fluoroquinolones (ciprofloxacin and levofloxacin) in uncomplicated UTIs due to increased risk of developing resistance and the high risk of mycobacterial tuberculosis infections in Sri Lanka for which these drugs are reserved as second line therapy.

1. Introduction

Urinary tract infections are the second most common bacterial infection worldwide, affecting approximately 400 million people annually [1]. UTIs are a significant public health concern in Sri Lanka. UTIs are classified according to severity (complicated vs uncomplicated) and location (upper urinary tract vs lower urinary tract).

Majority of UTIs are caused by uropathogenic *Escherichia coli* (UPEC) [2]. Other common causative bacteria are *Klebsiella pneumoniae*, *Proteus mirabilis*, *Enterococcus faecalis and Staphylococcus saprophyticus* [1]. Clinical presentation is diverse ranging from simple cystitis to urosepsis, posing challenges to management. In addition, differentiation of infection by the isolated organism from asymptomatic colonization is important. The emerging challenges in management of UTIs is the emergence of multidrug resistant strains and occurrence of recurrent infections, causing significant morbidity and increased health care costs. Literature reveals a high prevalence of extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae, AmpC beta lactamase and carbapenamase producing bacteria among patients with UTIs in Sri Lanka [3]. Patient factors such as female gender, indwelling urinary catheters, presence of comorbidities such as diabetes, anatomical or functional genitourinary abnormalities and immunocompromised states predispose to UTIs [4]. Prescribers need to consider the likely organism, severity of infection and the location of UTI, when selecting the most appropriate empirical antibiotic. The appropriate antibiotic should achieve adequate urinary concentrations and be efficacious against the likely pathogens based on local resistance data.

2. Classification of UTI

UTIs are classified as complicated or uncomplicated. In addition, identification of recurrence and specific populations such as catheter-associated infections need special consideration.

Uncomplicated UTI

This entity refers to UTIs in healthy, non-pregnant women without any urological abnormalities.

Complicated UTIs

Complicated UTIs refer to infections associated with factors that increase the risk of treatment failure or predispose to poor clinical outcomes. These factors include urinary tract abnormalities (e.g., obstruction, stones, neurogenic bladder), immunosuppression, diabetes mellitus, renal insufficiency, pregnancy or the presence of a foreign body such as a catheter. Although UTIs in men were considered as complicated previously, recent guidelines suggest that male UTIs without structural abnormalities or

comorbidities may not always be classified as complicated [5].

3. Guide to empirical antibiotic therapy

Majority of patients will require empirical antibiotics prior to targeting therapy based on microbiological results. The choice of antibiotic should be based on selecting a drug with a spectrum that covers the likely organism, while adhering to antibiotic stewardship practices. It is important to consider severity of the presentation, when selecting the empirical antibiotic in addition to local susceptibility patterns.

Lower urinary tract infections

Simple cystitis in non-pregnant women without any functional or anatomical urinary tract abnormalities or underlying comorbidities such as diabetes is mostly due to UPEC. This group of patients can be treated without a urine culture. Treatment with sustained release nitrofurantoin 100mg twice a day (or nitrofurantoin 100 mg 6 hourly if not sustained release) for 5 days or cephalexin 500mg twice a day for 3 days (Figure 1) is indicated [6]. Nitrofurantoin acts in acidic urine and an agent for urinary acidification such as vitamin C is combined for enhanced action.

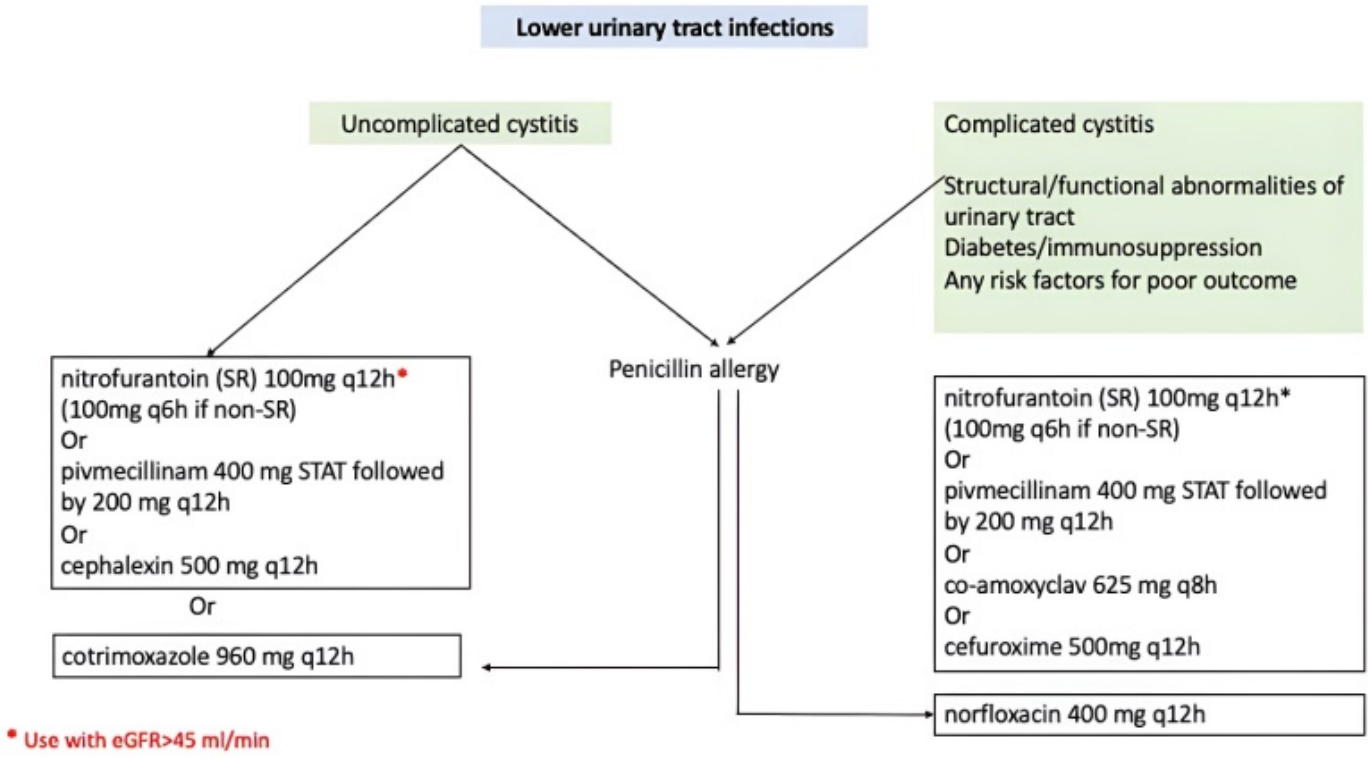

Figure 1: Lower urinary tract infections

If first line antibiotics are not appropriate (eGFR<45 ml/minute or penicillin allergy), cotrimoxazole 960 mg twice a day can be prescribed. Pivmecillinam, is a penicillin with a narrow-spectrum that is appropriate for lower urinary tract infections given as a 400mg initial dose followed by 200mg three times a day [5]. Patients with risk factors for a poor outcome (complicated cystitis) could be treated with co-amoxiclav 625 mg 8 hourly or cefuroxime 500 mg twice a day apart from the antibiotics mentioned above. Duration of treatment is extended to 7 days.

Pyelonephritis

Blood and urine cultures should be obtained in patients with pyelonephritis. Pyelonephritis in non-pregnant women without structural or functional abnormalities of the urinary tract, can be managed as outpatients with oral co-amoxiclav (Figure 2). Patients in sepsis with or without septic shock

should be managed with a combination of antibiotics to cover ESBL-producing Enterobacteriaceae. Combination could be piperacillin-tazobactam or carbapenem with an aminoglycoside (Figure 2). Of the available carbapenems in Sri Lanka, ertapenem has a narrow spectrum (with ESBL coverage) suitable for UTIs. Ertapenem is prescribed 1g once daily. Aminoglycoside therapy should be reviewed at 48 hours and antibiotics targeted according to blood and urine culture results. A combination (coamoxiclav/3rd generation cephalosporin with aminoglycoside) is considered for patients with a suspicion of infection with a resistant organism (previous culture result) or structural abnormalities of the urinary tract. Ciprofloxacin should be used in the presence of beta-lactam hypersensitivity. Treatment duration is 10-14 days for pyelonephritis. Interventions such as inserting stents to relieve obstruction should be considered in severe infections secondary to urinary tract obstruction.

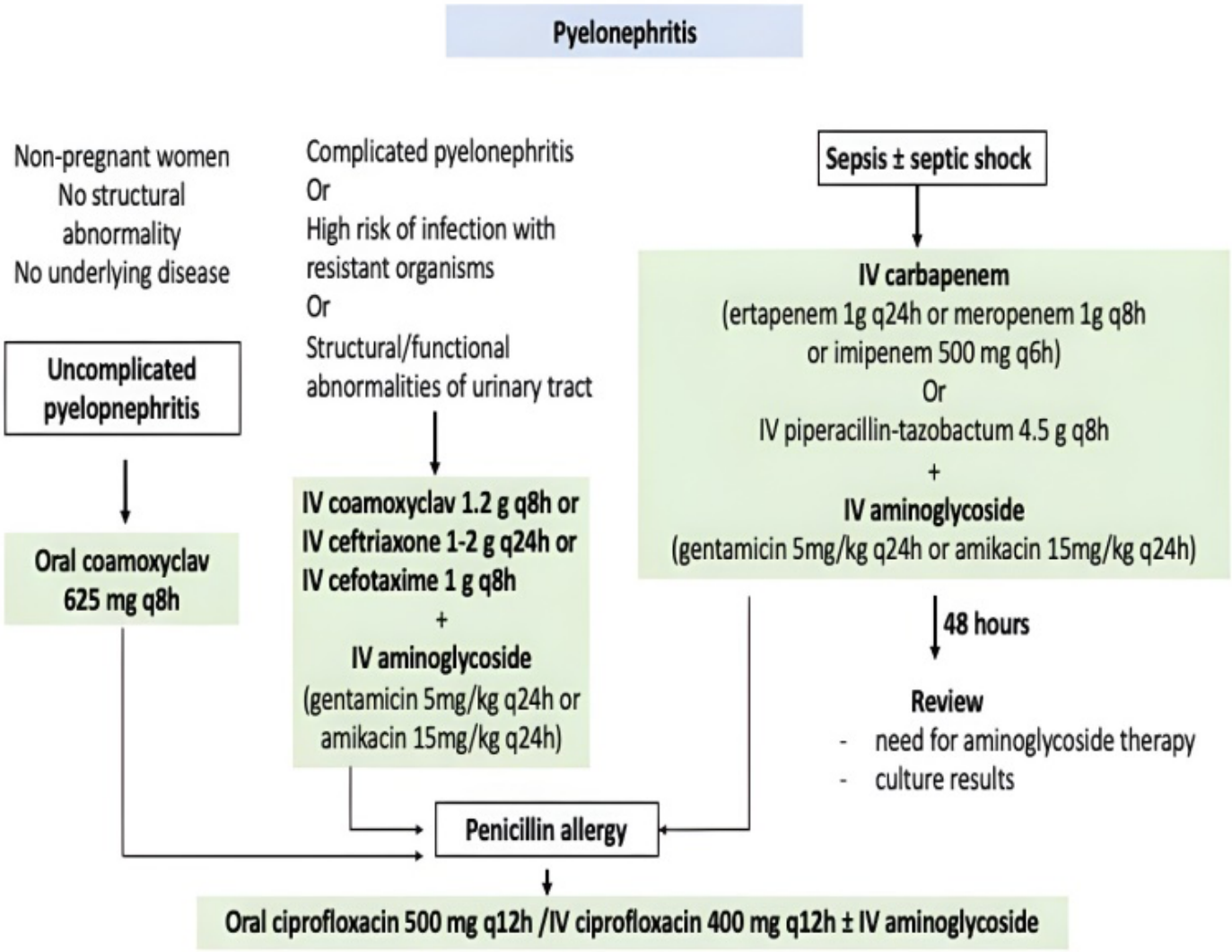

Figure 2: Treatment of pyelonephritis

Recurrent UTIs

Recurrent UTIs are defined as the occurrence of two or more infections in six months or three or more infections in a year. Asymptomatic bacteriuria should not be treated unless the patient is undergoing a urological procedure or pregnant. It is important to avoid unnecessary antibiotics in this group and treatment to be guided by the presence of symptoms. A cause for recurrence should be sought

in all patients which could be structural abnormalities or neurogenic bladder.

Catheter-associated UTI (CAUTI)

CAUTIs occurring in patients with indwelling urinary catheters or those undergoing intermittent catheterization, should be guided by cultures. Empirical antibiotic therapy is similar to non-CAUTI in lower urinary tract involvement. In CAUTI causing pyelonephritis, a broader coverage could be considered at the onset (Figure 1). Sepsis will be treated similar to a patient without an indwelling catheter.

Candiduria

Candiduria is a common finding in the presence of patient risk factors such as uncontrolled diabetes mellitus, indwelling catheters and prior antibiotic therapy. It does not warrant antifungal therapy in patients with normal immune systems and management should focus on correction of underlying risk factors.

Conclusions

Effective management of UTIs requires a strategic approach considering the appropriate antibiotic selection, antimicrobial stewardship, and individualized patient care. The rising prevalence of multidrug-resistant organisms, including ESBL- and carbapenemase-producing bacteria, underscores the need for judicious antibiotic use and adherence to local resistance patterns. While uncomplicated UTIs can often be managed with short-course, narrow-spectrum antibiotics, complicated infections demand careful evaluation and targeted therapy based on microbiological results. Preventing recurrent infections through risk factor modification and avoiding unnecessary antibiotic use remain critical components of care. As resistance patterns evolve, continuous surveillance, updated treatment guidelines, and research into alternative therapies will be essential to optimizing UTI management in Sri Lanka.

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Dr Nilanka Perera
MBBS, MD [Medicine], MRCP [UK],
Senior lecturer, Department of Medicine, Faculty of Medical Sciences, University of Sri Jayewardenepura and Consultant Physician
Email: nilanka@sjp.ac.lk

N. Shirani Chandrasiri
MBBS, MD [Medical Microbiology],
Senior Lecturer, Department of Microbiology and Parasitology, Faculty of Medicine, University of Moratuwa
Email: shiranin4@gmail.com

Guidelines on management of haemophilia A and the use of Factor VIII

Introduction

Factor VIII (FVIII) was first discovered in 1937. It was only after four decades that purified factor VIII was developed. Purified FVIII concentrates are used to prevent and treat bleeding in hemophilia A and other causes of factor VIII deficiency. It has two varieties, which are the more commonly used; plasma derived higher purity FVIII concentrates and the plasma derived FVIII concentrates containing variable amount of von Willebrand factor. The latter is more commonly used in treatment of von Willebrand disease, although it can be used in haemophilia A when higher purity FVIII products are in short supply [1].

The cloning of the factor VIII gene led to the production of recombinant human factor VIII (rFVIII). Recombinant factor VIII does not carry the risk of transmitting blood-borne viruses as it does not contain plasma or albumin. rFVIII are found as standard half-life recombinant FVIII concentrates (SHL-rFVIII) and Extended half-life recombinant FVIII concentrates (EHL-rFVIII) [1]. EHL-rFVIII stays in the blood for a longer period enabling a reduced frequency of injections.

Purified FVIII can give rise to many adverse effects based on hypersensitivity to any remaining contaminating components in plasma. These may range from erythema of the skin to hypotension and wheezing.

On the contrary rFVIII products are associated with a higher risk of inhibitor development than plasma-derived FVIII products due to it's specificity for FVIII compared to plasma-derived FVIII.

The burden on health care

Haemophilia burdens the health budget due to the need for regular replacement of coagulation factors and the life-long nature of the disease [1]. Due to the high cost of products required for the treatment of coagulation disorders, it is imperative that available resources are used optimally and in the most efficient manner.

The need for comprehensive care

Haemophilia is a rare inherited disorder that is complex to manage. Comprehensive care goes beyond the treatment of acute bleeding. Implementing comprehensive care will reduce the amount of FVIII needed for treatment of patients. Some aspects of comprehensive care include [2].

- Prevention of bleeding
- Prompt management of bleeding episodes
- Prevention and management of inhibitor development
- Patient/family /caregiver education
- Availability of emergency care

Principles of care and general management

1. The primary aim of care is to prevent and treat bleeding with the deficient clotting factor.
2. Acute bleeds should be treated as quickly as possible, preferably within 2 hours. If in doubt, treat as for FVIII deficiency.
3. Patients usually recognize early symptoms of bleeding even before the manifestation of physical signs. This is often described as a tingling sensation or "aura".
4. P.R.I.C.E. regimen (see below) is an essential part of treating acute joint/muscle bleeds
5. Veins must be treated with care. They are the lifelines for a person with haemophilia.
    - 23- gauge or 25-gauge butterfly needles are recommended.
    - Never cut down into a vein, except in an emergency.
    - Apply pressure for 3–5 min after venipuncture.
    - Venous access devices should be avoided whenever possible but may be required in some children.
6. Regular exercise and other measures to stimulate normal psychomotor development should be encouraged to promote strong muscles, develop balance and coordination, and improve fitness.
7. Patients should avoid activities likely to cause trauma.

8. Drugs that affect platelet function, particularly aspirin and non- steroidal anti-inflammatory drugs (NSAIDs), except certain cyclooxygenase 2 (COX-2) inhibitors, should be avoided. Paracetamol / is a safe alternative for analgesia.
9. Factor levels should be raised to appropriate levels prior to any invasive procedure.
10. Good oral hygiene is essential to prevent periodontal disease and dental caries, which predispose to gum bleeding. In Children with haemophilia, referral to a dental care centre at the time of first tooth eruption or before the age of one year is recommended.
11. Vaccination -
    - Children and adults with haemophilia should be administered the age-appropriate routine vaccines as the general population.
    - Should preferably receive the vaccines subcutaneously rather than intramuscularly or intradermally (Subcutaneous route is as safe and effective as the latter and does not require clotting factor infusion).
    - If intramuscular injection must be the route of administration, a 20% correction of clotting factors should be given prior to the vaccination, and vaccination should be with the smallest gauge needle available (25-27 gauge). A dose of tranexamic acid can be given prior to vaccination, preferably starting from the previous night and continuing 8 hourly for 24 hrs. Additionally, an ice pack should be applied to the injection site for 5 minutes before the injection. Pressure should be applied to the site for at least 10 minutes to reduce bleeding and swelling.

The severity of bleeding in haemophilia is generally correlated with the clotting factor level, as shown in Table 1. Recommended FVIII doses and duration of administration for Haemophilia A is shown in Table 2.

The treatment of some specific haemorrhages needs special attention.

Joint haemorrhage (Haemarthrosis)

- Look for early signs that should alert patients and carers such as rapid loss of range of motion of the joint, or pain or an unusual (tingling) sensation in the joint which is known as “aura” of a bleed.
- Palpable swelling and warmth of the skin over the joint, is considered a late recognition.
- Administer clotting factor concentrate immediately- 10-20IU/kg (20-40%) and repeat if clinically indicated.
- Manage associated pain with analgesics determined by the severity of pain.
- Use adjunctive therapy- PRICE regimen, tranexamic acid and arthrocentesis if indicated.
- Begin physiotherapy as soon as pain subsides as a part of rehabilitation.

Table 1: Relationship of bleeding severity with clotting factor level

Severe	<1 IU/dL or <1% of normal	Spontaneous bleeding into joints or muscles, predominantly in the absence of an identifiable haemostatic challenge
Moderate	1 – 5 IU/dL or 1 – 5% of normal	Occasional spontaneous bleeding; prolonged bleeding with minor trauma or surgery.
Mild	5 – 40 IU/dL or 5 – <40% of normal	Severe bleeding with major trauma or surgery. Spontaneous bleeding is rare.

Table 2: Recommended factor VIII doses and duration of administration for Haemophilia A in Sri Lanka [1]

Type of haemorrhage/ indication	Factor correction	Dose of Factor VIII	Frequency	Duration in days
Joint	20-40 %	10-20 IU/kg	daily/bd	1-2
Muscle	20-40 %	10-20 IU/kg	daily/bd	2-3
Iliopsoas	40-80 % 20-40 %	20-40 IU/kg 10-20 IU/kg	bd daily or bd	D1 D2-D5
CNS	100% 60-80% 40-60%	50 IU/kg 30-40 IU/kg 20-30 IU/kg	bd daily or bd daily	D1-D3 D4-D7 D8-D14
Throat and neck	60-80% 20-40%	30-40 IU/kg 10-20 IU/kg	bd daily or bd	D1-D3 D4-D7
Gastrointestinal	60-80% 20-40%	30-40 IU/kg 10-20 IU/kg	bd daily or bd	D1-D3 D4-D7
Haematuria	Hydration 30-60%	- 15-30 IU/kg	- daily/bd	D1-D2 D3-D5
Major surgery/ trauma	60-80% 50-70% 20-50%	30-40 IU/kg 25-35 IU/kg 10-25 IU/kg	Just prior * bd bd daily	Pre-op / D1 D2-D3 D4-D10
Minor surgery	40-60% 20-30% 20-30%	20-30IU/kg 10-15 IU/kg 10-15 IU/kg	Stat bd daily	Pre-op D1 D2-D5
Suture removal	30%	15 IU/kg	Stat	Pre-procedure
FNAC	30%-50%	15 -25IU/kg	Stat	Pre-procedure
Dental –Molar Other	50% 30%	25 IU/kg 15 IU/kg	Stat Stat	Pre-procedure Pre-procedure

Muscle haemorrhage

- Early signs that should alert include aching of the muscle, tendency to maintain the limb in a position of comfort, severe pain if the muscle is stretched, increasing pain if the muscle is made to actively contract and tension, tenderness upon palpation and possible swelling.
- Raise the patient's factor level as soon as possible, ideally when the patient recognizes the first signs of discomfort or after trauma.
- If there is neurovascular compromise, maintain the levels for 5–7 days or longer, determined by the persistence of symptoms.
- Repeated infusions are often required for 2–3 days or much longer in case of bleeds at critical sites causing compartment syndromes and if extensive rehabilitation is required.
- The patient should be monitored continuously for neurovascular compromise; fasciotomy may be required in some such cases.
- Physiotherapy should begin as soon as pain subsides and should be progressed gradually to restore full muscle length, strength, and function.

Central nervous system haemorrhage or trauma to the head

- This is a medical emergency. Treat first before evaluating.
- Immediately raise the patient's factor level when significant trauma or early symptoms occur. Further doses will depend on imaging results. Maintain FVIII level until aetiology is defined.
- If a bleed is confirmed, maintain the appropriate factor level for 14 –21 days.
- Intracranial haemorrhage may be an indication

for prolonged secondary prophylaxis (3–6 months), especially where a relatively high risk of recurrence has been observed.

Calculation of the dose of FVIII for treatment

- The dose is calculated by multiplying the patient's weight in kilograms by the factor level desired in IU/dL, divided by 2.

  Example: 50 kg patient with factor level <1%, desired level 40 IU /dL Requirement: (50x40)/2=1,000 units of FVIII per dose.
- Refer to table 2 above for suggested factor level and duration of replacement required based on type of haemorrhage.
- Doses should be rounded up to the **nearest vial size**. Do not discard any product (use the whole vial**).** E.g. 20 kg child requiring 30 units/kg factor VIII, give 750 units.
- Subsequent doses and frequency of administration for a particular product should ideally be based on the half-life of FVIII and on the recovery in an individual patient.

If the bleeding does not stop

Administer the appropriate dose of FVIII concentrate to raise the patient's factor level suitably. If the bleeding does not stop, a second infusion maybe required. If so, repeat half the initial loading dose in 12 hours (haemophilia A) or 24 hours (haemophilia B). Prompt and precise treatment reduces morbidity and mortality. It will also reduce the amount of factor VIII needed for a given patient. Knowledge on treatment of specific haemorrhages and principles of care and general management is important.

Prophylactic factor replacement therapy

Prophylaxis is the continuous replacement therapy of the missing clotting factor to prevent anticipated bleeding. It is only recommended haemophilia patients with FVIII level less than 1% or phenotypically severe haemophilia with a high annual bleeding rate. After an intracranial bleed, prophylaxis should be started immediately.

The decision to administer prophylactic therapy should be made by ~~a~~ consultant haematologist [1]. Either the patient or caregivers should be taught to maintain timely and accurate records of bleeding episodes and treatment administered [2]. Prophylaxis is cost-effective in the long term because it eliminates the high cost associated with subsequent management of damaged joints and improves quality of life. Breakthrough bleeds should be treated based on the site and severity until complete resolution of the bleed. The prophylactic regimen should be reviewed appropriately [1].

With the availability of EHL-rFVIII concentrates, the clinical outcome of prophylaxis has improved during recent past, due to need of less frequent infusions, resulting in improved adherence to therapy. The prophylactic dose should be rounded up to the nearest whole vial size. Prophylaxis is best given in the morning to cover periods of activity. The types of prophylaxis in haemophilia are depicted on table 3.

Table 3: Types of prophylaxis in haemophilia

Primary prophylaxis	Regular continuous treatment initiated in the absence of documented osteochondral joint disease and started before the second clinically evident large joint bleed and three years of age.
Secondary prophylaxis	Regular continuous treatment started after bleeds into large joints and before the onset of joint disease.
Tertiary prophylaxis	Regular continuous treatment started after the onset of joint disease.
Intermittent ("Periodic")	Treatment given to prevent bleeding for periods not exceeding 45 weeks in a year. (to interrupt bleeding cycles / to cover higher risk of injury)

Inhibitors to exogenous coagulation factors

In haemophilia A patients, inhibitors refer to IgG alloantibodies to exogenous clotting factor VIII (FVIII)) that would neutralize the function of infused clotting factor concentrates (CFC). Patient with haemophilia who fail to respond clinically to CFC replacement therapy should alert as to the presence of a new inhibitor. Inhibitors are more frequently encountered in patients with severe disease. Controlling bleeds is a greater challenge in the patient who has developed inhibitors.

Considering the complexity of this serious complication the patient and family or caregiver education and psychosocial support become essential components of management. It is vital for the clinicians, patients, caregivers, and the haemophilia treatment centre team to maintain good communication with one another [2].

Immune toleration induction is recommended for patients with severe haemophilia A and presence of a persistent inhibitor that interferes with prophylaxis or treatment of bleeds at standard doses of FVIII [1].

The ultimate goal in the treatment of inhibitors development in congenital haemophilia is to induce immune tolerance (IT). It is clear that it is possible to achieve IT induction with both recombinant products and human-derived products [3].

Patient, family and caregiver education

People with haemophilia and family or primary caregivers must receive comprehensive education on haemophilia care, particularly on the prevention and treatment of bleeds and management of musculoskeletal complications, and training on essential skills for self-management which includes bleed recognition, self-treatment, record-keeping and dental care [2].

The following policies need to be implemented for efficient and optimal use of Factor VIII

- Consultant or specialist physician to authorize Factor VIII requests to ensure compliance with the criteria outlined.
- In case of requests for factor VIII that are not in accordance with these guidelines, approval MUST be obtained from a consultant haematologist or a specialist physician.
- An additional dose to be considered during surgery depending on the duration or blood loss
- Infusions for routine prophylaxis for a given unit should be planned on one day for optimal use of FVIII
- Prioritization of indications by the consultant, may be relevant in some situations
- Monitoring the usage of FVIII by filling a form sent by the pharmacy for each patient administered FVIII.
- Pharmacists are requested to maintain consumption data of each unit, by collecting the forms filled on FVIII usage in each patient.
- Data on donations of Recombinant FVIII concentrates and plasma derived FVIII will be maintained separately.
- The Medical Supplies Division to monitor data consumption data at the Health Ministry level.

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Dr. S. A. F. Kurukulasuriya*
MBBS(Col) MD(Medicine)
Senior Lecturer in Pharmacology Gr.I
skurukulasuriya@kln.ac.lk

Dr. C. S. Thevarapperuma*
MBBS(Col), DPath, MD (Haematology)
Consultant Haematologist
csthevar@yahoo.com

*Representing the Guideline Development Group

This guideline was developed by the Sri Lanka Association of Clinical Pharmacology and Therapeutics (SLACPT) in consultation with the Sri Lanka College of Haematologists

Deprescribing antihypertensive drugs in frail older adults

SUMMARY

Antihypertensive drugs are commonly used by older adults because of the high prevalence of cardiovascular disease and its risk factors, and the increased absolute benefit of blood pressure reduction with increasing age. Clinical trials of blood pressure reduction in older adults have generally excluded older adults with multimorbidity, frailty and limited life expectancy. In this population, the benefit–harm ratio of aggressive blood pressure lowering may become unfavourable; a more relaxed blood pressure target may be appropriate; and deprescribing (cessation or dose reduction) of one or more antihypertensive drugs can be considered. Before deprescribing an antihypertensive drug, it is important to consider other indications for which it may have been prescribed (e.g. heart failure with reduced ejection fraction, diabetic nephropathy, atrial fibrillation). Evidence from randomised controlled deprescribing trials indicates that it is possible to deprescribe antihypertensives in frail older people. However, some patients may experience an increase in blood pressure that warrants restarting the drug. There are limited data on long-term outcomes (follow-up in deprescribing trials ranged from 4 to 56 weeks). The risk of adverse outcomes associated with deprescribing, such as withdrawal effects, can be minimised through appropriate planning, patient engagement, dose tapering and monitoring.

Keywords

antihypertensive drugs, deprescribing, frailty, hypertension, older adults, polypharmacy

(Aust Prescr 2024;47:85–90)

Introduction

Antihypertensive drugs, and often more than one, are commonly used by older adults (65 years and over) because of the high prevalence of cardiovascular disease and its risk factors in this population, and the increased absolute benefit of blood pressure reduction with increasing age.[1] In most older people there are good reasons to continue antihypertensive therapy, but in some cases the benefits of continued prescribing may not outweigh the harms. This is most likely in people who are frail (increased vulnerability to stressors due to decline in reserve and function across multiple physiological systems),[2] or whose goals of care have changed because of limited life expectancy. In this group, blood pressure targets may be relaxed and deprescribing (dose reduction or cessation) of one or more antihypertensive drugs may be considered.[1,3]

Observational studies in residential aged care and hospital wards have reported that deprescribing antihypertensives occurs in 11 to 41% of frail older people with low blood pressure and either a history of falls, advanced dementia or limited life expectancy.[4-6] The aim of this article is to discuss when deprescribing antihypertensives may be considered in frail older adults, and how the general principles of deprescribing apply to antihypertensives.

Decisions on deprescribing of antihypertensive drugs must consider all the indications for which they are prescribed, including heart failure, diabetic nephropathy and atrial fibrillation. The focus of this article is on frail older adults who are using antihypertensive drugs to lower blood pressure or for primary prevention of cardiovascular disease, as the evidence base for deprescribing is mainly in this group.

Evidence for lowering blood pressure in older adults

Hypertension is a major modifiable risk factor for cardiovascular events and mortality in older people. Australian and international clinical guidelines recommend that blood pressure should be controlled in people at high risk of cardiovascular disease, unless contraindicated or clinically inappropriate,[7,8] owing to the established benefit in preventing cardiovascular events and reducing mortality.[9,10]

There is no chronological age above which antihypertensive drugs are contraindicated. Randomised controlled trials have reported that lowering elevated blood pressure in older people reduces the risk of cardiovascular events and death, including in people aged over 80 years.[11,12]

However, trials of antihypertensive drugs in older adults have generally been conducted in fitter and healthier populations than many of the people who are prescribed these drugs in practice.[13] For example, people with dementia, with limited life expectancy or living in residential care were excluded from pivotal studies of antihypertensives that recruited older people.[11,12] There is limited evidence about the benefits of ongoing antihypertensive therapy in complex older adults with multimorbidity, polypharmacy and frailty.[3,13-15]

Balancing the benefits and harms of antihypertensive drugs in frail older adults

Antihypertensive drugs can contribute to drug-related harms (e.g. falls, syncope, electrolyte disturbances, acute kidney injury), particularly in older adults with multimorbidity, polypharmacy and frailty.[3,16] Specific adverse effects vary by antihypertensive medication class and have been summarised elsewhere.[17]

Patients may be started on antihypertensive drugs when they are younger (often in their 40s to 60s), but the balance of potential benefits and harms can change over the ensuing decades with changing physiology, comorbidities, concomitant medicines and goals of care, such that the balance of benefits to harms may eventually become unfavourable. Sometimes an antihypertensive drug that was once appropriate may become a candidate for deprescribing.[15,18]

What is deprescribing?

Deprescribing is the process of trialling dose reduction or cessation of a medication where the current risk of harm outweighs the potential benefit for the individual, supervised by a clinician, with the goal of improving outcomes.[19] It does not include temporary cessation, such as withholding an antihypertensive drug because of intercurrent illness (e.g. low blood pressure due to sepsis).

Evidence for deprescribing antihypertensive drugs

There is a small but growing body of evidence examining the feasibility and safety of deprescribing antihypertensives in older adults. While the short-term evidence is supportive, there is uncertainty regarding the longer-term benefits and harms.[20]

A Cochrane review of 6 randomised controlled deprescribing trials (total 1073 participants, followed up for 4 to 56 weeks) reported that it may be feasible to stop one or more antihypertensive drugs used for hypertension or primary prevention of cardiovascular disease in adults aged 50 years and older. Up to one-third of participants in the deprescribing group (compared with up to 15% in the continuation group) experienced raised blood pressure or other clinical criteria that required restarting of therapy or removal from the study. Systolic blood pressure was higher in the deprescribing group than the continuation group (mean difference 9.75 mmHg). The impact of deprescribing antihypertensive drugs on cardiovascular events and all-cause mortality was uncertain; odds ratios for these outcomes were increased in the deprescribing group compared with

the continuation group, but with wide confidence intervals dipping below 1.0.[21] No studies included in the review reported the frailty of participants.

The Optimising Treatment for Mild Systolic Hypertension in The Elderly (OPTIMISE) study was a randomised controlled deprescribing trial, published after the Cochrane review. It involved 569 patients over 80 years old with clinic systolic blood pressure lower than 150 mmHg who were using 2 or more antihypertensive drugs and, in the investigators' opinion, could potentially benefit from medication reduction due to polypharmacy, comorbidity, nonadherence or frailty. Patients were randomised to cessation of one antihypertensive drug using a deprescribing algorithm, or to standard care. There was no difference between the groups in the proportion of patients who maintained systolic blood pressure below 150 mmHg at 12 weeks follow-up, and no difference in serious adverse events or healthrelated quality of life. Systolic blood pressure was 3.4 mmHg higher in the deprescribing group than the continuation group, and medication reduction was sustained in 66.3% of patients.[22]

In an Australian observational study of 239 frail older people who had an unplanned hospital admission and were discharged to a nursing home, 44 patients (18.4%) had 52 antihypertensive drugs ceased in hospital. Deprescribing was not limited to drugs that had been prescribed for hypertension or primary prevention of cardiovascular disease (indications were not reported). Patients who had antihypertensive drugs deprescribed had increased 90-day mortality (adjusted odds ratio 2.27, 95% confidence interval 1.00 to 5.12, p=0.05) compared with those without deprescribing. The authors suggested this outcome could be due to residual confounding by indication. For example, older people with low blood pressure are likely to have antihypertensive medications ceased or reduced, and these patients are also known to have higher mortality than older people with normal or high-normal blood pressure. Blood pressure measurements before and after deprescribing were not reported.[6]

When to consider deprescribing antihypertensive drugs

There is limited evidence to guide decisions about when to deprescribe antihypertensive drugs. While current Australian and international guidelines recommend a blood pressure target of less than 140/90 mmHg when managing hypertension,7 tight blood pressure control may not be appropriate in some older adults because of changes in physiology and sequalae of harms (e.g. outcomes of a fall). Some studies have reported an increased risk of cardiovascular events in older adults with very low systolic (less than 120 mmHg) or diastolic (less than 65 mmHg) blood pressure.[17] The STOPPFrail tool, developed through an expert consensus process, recommends a systolic blood pressure target of 130 to 160 mmHg in older adults who are frail and have limited life expectancy.[23]

The 2023 European Society of Hypertension Guidelines for the management of arterial hypertension recommend 'Reduction of [antihypertensive] treatment can be considered in patients aged 80 years or older with a low systolic blood pressure (less than 120 mmHg) or in the presence of severe orthostatic hypotension or a high frailty level'.[8] They note that antihypertensive deprescribing should be conducted with caution because of a lack of data on the optimal process and likely outcomes.[8]

In lieu of strong evidence on who is suitable for deprescribing antihypertensives, clinicians can be guided by factors that increase risk of harm or signal a decrease in benefit or necessity of the medication, such that potential harms outweigh the benefits.

Review of antihypertensive drugs needs to be undertaken in the context of the patient's overall

medication regimen and current symptoms. There may be other medicines contributing to the patient's adverse effects or risk of harm that could be a higher priority for deprescribing (e.g. psychotropic drugs). Deprescribing requires considering the individual's preferences, values and treatment goals.[24-27]

Table 1 provides a protocol for identifying patients in whom it may be appropriate to deprescribe antihypertensive drugs, and individualising deprescribing, based on the CEASE framework.[28]

How to deprescribe

The risk of adverse outcomes when deprescribing, such as withdrawal effects, can be minimised or prevented through appropriate patient engagement, planning, tapering, monitoring and clinical handover.[17,18,20,29,30] If there are other prescribers involved in the patient's care (e.g. a cardiologist), they should also be engaged in deprescribing decisions.

Engage the patient and carer

Engaging the patient and their carer, if relevant, is essential for the process and the success of deprescribing.[31] Key points for discussion include:

- goals of care and preferences
- current experiences with antihypertensive drugs (e.g. tolerability, burden, possible adverse effects)
- why the drug is suitable for deprescribing (e.g. no longer of benefit, reduction of harms)
- identifying and addressing any fears about deprescribing
- emphasising that deprescribing is a trial, with a plan for monitoring and restarting the drug if necessary
- how to recognise and respond to any withdrawal symptoms
- intrinsic and extrinsic factors that can influence blood pressure (e.g. weather, illness, other medications), which means their antihypertensive regimen may need to be adjusted over time
- advice on modifiable lifestyle cardiovascular disease risk factors where appropriate.

Decide which antihypertensive drug(s) to deprescribe

The CEASE framework (Table 1) can help with deprescribing decisions. After obtaining a complete medication history, consider the indications and evidence for cardiovascular benefits for each of the patient's antihypertensive drugs, including whether there are any other indications (e.g. angiotensin converting enzyme inhibitors for diabetic nephropathy or heart failure) that could warrant continued treatment. Next consider harms that may be related to specific drugs, such as thiazide diuretics exacerbating gout.

Individual patient perceptions, preferences and priorities for the choice and order of drugs for withdrawal are likely to be major determinants of the success of deprescribing. In some cases, where there is an ongoing indication for blood pressure lowering but the patient has an adverse reaction to a specific antihypertensive, switching to a different antihypertensive may be more appropriate than deprescribing.

Deprescribe one drug at a time

One antihypertensive should be reduced or stopped at a time unless there is an urgent need to stop more than one. Adverse drug withdrawal events are less likely, and easier to attribute to a specific drug, if deprescribing occurs one drug at a time. Where possible, patients on a fixed-dose combination antihypertensive should be converted to individual drugs to facilitate deprescribing one drug at a time. There may be circumstances when deprescribing more than one antihypertensive drug concurrently is appropriate; for example, if the patient is experiencing significant adverse effects related to the overall regimen (e.g. severe hypotension). This should usually occur in a supervised setting with close monitoring (e.g. in hospital).

Table 1: Deprescribing protocol for antihypertensive drugs based on the CEASE framework[28]

Steps	Description	Considerations
C: current drugs	Ascertain all drugs the patient is currently taking and their indication(s)	• Indication(s) for the patient's antihypertensive drug(s): - caution required if there is an indication other than hypertension (e.g. heart failure with reduced ejection fraction, diabetic nephropathy), evidence of target organ damage, or a history of secondary or malignant hypertension • Current blood pressure and individualised target: - consider patient's comorbidities, frailty severity, life expectancy, and treatment goals and preferences [NB1] • Other drugs that may affect blood pressure (e.g. sodium-glucose co-transporter 2 inhibitors) or increase the risk of harm (e.g. drugs that increase falls risk)
E: elevated risk	Consider if the patient is at elevated risk of (or experiencing) harm from any of their drugs	• Antihypertensive adverse effects, including: - drug- or class-specific adverse effects (e.g. oedema with calcium channel blockers) - symptoms related to low blood pressure or orthostatic hypotension (e.g. light-headedness, dizziness) [NB2] [NB3] • Prescribing cascades (where a drug is prescribed to manage the adverse effects of another drug). For example: - antihypertensive prescribed following initiation of a nonsteroidal anti-inflammatory drug - drugs prescribed for gout in a person using a thiazide diuretic • Drug–drug interactions
A: assess	Assess the current benefit to harm ratio for each drug	• Strength of indication(s) (likely benefits) for each drug • Presence and severity of existing adverse effects • Risk of future harm associated with continuing treatment: - consider patient factors that may increase risk, such as frailty, impaired cognition, comorbidities, medication nonadherence and other drugs
S: sort and prioritise	Prioritise drugs for deprescribing, according to benefit, harm, ease of stopping and patient preference	• When multiple antihypertensive drugs are being used, prioritise drug(s) with the weakest indication or highest risk of harm
E: eliminate	Implement a discontinuation regimen, and monitor closely for withdrawal syndromes or rebound symptoms that may require restarting treatment	• Usually one drug should be reduced or stopped at a time • The deprescribing regimen (e.g. rate of taper) should take into consideration: - urgency of deprescribing (e.g. whether there are existing adverse effects) - risk of withdrawal syndrome - availability of monitoring (withdrawal may be done more rapidly in a hospital or aged-care setting) - practicality of tapering (e.g. whether the person or their carer can manage a complex tapering regimen) • Monitor for changes in blood pressure and adverse drug withdrawal effects

NB1: There is limited evidence to guide the selection of an optimal blood pressure target for frail older adults. The target range needs to be individualised based on the person's goals of care, and assessment of potential benefits and harms. As a guide, the STOPPFrail consensus tool for identifying potentially inappropriate medicines in frail older adults with limited life expectancy recommends a systolic blood pressure target of 130 to 160 mmHg.[23] Systolic blood pressure below 120 mmHg, and diastolic blood pressure below 60 mmHg, should be avoided in frail older adults.[3,8,17]
NB2: Orthostatic hypotension is defined as more than a 20 mmHg fall in systolic blood pressure or more than a 10 mmHg fall in diastolic blood pressure on standing.
NB3: Not all antihypertensive drugs are associated with orthostatic hypotension.[1]

Taper the dose

In most cases, antihypertensive doses should be tapered before stopping the drug.[17,18,20,29,30] Abrupt cessation of beta blockers can lead to a rebound phenomenon of angina, anxiety, severe hypertension, tachycardia and can cause a myocardial infarction. Clonidine can also cause a withdrawal syndrome if it is not tapered. While the other classes of antihypertensive drugs have not been clearly associated with withdrawal effects, abrupt cessation can lead to rapid return of hypertension, or in the case of diuretics, fluid accumulation.[17,20,29,30]

Tapering also enables identification of the lowest effective dose if the drug cannot be completely stopped. Additionally, tapering may encourage patient acceptance of, and comfort with, deprescribing.[31]

Although there is limited evidence to guide the process of deprescribing antihypertensive drugs, a general approach is to taper the dose by 25 to 50% every 4 weeks. A faster rate of taper or immediate cessation may be required if the patient is experiencing adverse reactions to antihypertensive treatment, and there is a low risk of drug withdrawal effects or a high level of supervision with close monitoring is available.

Written instructions and adherence aids are often required to support complex deprescribing regimens. Currently there are no widely available patient resources for deprescribing antihypertensives, but resources for other drug classes could be adapted.[21,32]

Monitor outcomes and provide clinical handover

Monitor blood pressure and watch for symptoms of withdrawal or rebound at every tapering step. Continue to closely monitor blood pressure for at least 4 weeks after cessation, followed by ongoing routine monitoring. The frequency and method of ongoing monitoring should be individualised based on the patient's treatment goals.[8,10]

Document the deprescribing plan and outcomes in the patient's medical record and clinical handover summary where relevant. This should include the reason for deprescribing, the targeted drug(s), the tapering schedule, the monitoring plan, and the threshold for reinstating therapy.

Conclusion

Antihypertensive drugs have established benefits in cardiovascular disease risk reduction in older adults. Use of multiple antihypertensives is common and, while this can be appropriate and beneficial in many cases, their continuation should be regularly reviewed. Deprescribing one or more antihypertensive drugs may be considered when the potential benefits are outweighed by the risk of harms, or no longer align with the patient's goals of care.

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Emily Reeve: Senior Research Fellow and NHMRC Emerging Leadership Fellow, Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University and Affiliate Senior Research Fellow, Clinical and Health Sciences, University of South Australia, Adelaide.

Danijela Gnjidic: Associate Professor, School of Pharmacy, Faculty of Medicine and Health, The University of Sydney.

Aili V Langford: NHMRC Emerging Leadership Fellow1 Adjunct Senior Lecturer, Sydney School of Public Health, Faculty of Medicine and Health, The University of Sydney.

Sarah N Hilmer: Head of Department of Clinical Pharmacology, and Senior Staff Specialist in Aged Care, Royal North Shore Hospital, Sydney and Conjoint Professor, Geriatric Pharmacology, Faculty of Medicine and Health, The University of Sydney and Kolling Institute, Sydney.

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