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Review article

Sodium glucose-linked transport protein 2 inhibitors: An overview of genitourinary and peri-operative implications

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Abstract

Sodium glucose-linked transport protein 2 inhibitors are relatively novel drugs, used for the treatment of Type 2 Diabetes Mellitus. Their usage since Pharmaceutical Benefits Scheme approval in Australia has increased drastically, possibly due to the low risk of hypoglycemic events and their advertised cardiovascular mortality benefits. However, as with any novel drug, adverse effects regarding their use requires medical practitioner awareness for optimal patient outcomes. This paper will aim to cover the major urological implications, including those pertinent peri-operatively that concern this class of drugs. There is a clear risk in developing genital mycotic infections with the use of sodium glucose-linked transport protein 2 inhibitors, including serious infections such as Fournier's Gangrene. Evidence for developing urinary tract infections have been mixed. Sodium glucose-linked transport protein 2 inhibitor induced lower urinary tract symptoms may have impacts on quality of life via increased reports of pollakiuria and nocturia. Peri-operative

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usage increases risk of euglycemic diabetic ketoacidosis. It is recommended that Sodium glucose-linked transport protein 2 inhibitors be ceased peri-operatively.

Keywords: diabetic ketoacidosis, hypoglycemic agents, lower urinary tract symptoms, urinary bladder overactive, urinary tract infections

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Introduction

Sodium glucose-linked transport protein 2 inhibitors (SGLT2i) are a relatively new class of drugs for the treatment of Type 2 Diabetes Mellitus (T2DM), that act on the proximal convoluted tubules of the nephrons to prevent resorption of glucose from the filtrate[1]. Approximately 90% of the renal reabsorption of filtered glucose occurs in the proximal convoluted tubules via SGLT2 channels, with the sodium glucose-linked transport protein 1 mechanism accounting for less than 10%[2]. In T2DM, there can be an unwanted response where SGLT2 expression can be upregulated due to higher renal serum glucose threshold, making this receptor an ideal target for anti-hyperglycemic treatment[2].

Large scale studies with empagliflozin (EMPA-REG trials) have demonstrated cardiovascular mortality benefits via significant reductions in relative risk when compared to placebo, which include reductions by 38% for cardiovascular death, 35% in preventing hospitalization due to heart failure, as well as by 32% for death from all causes [3]. Other findings of the study include reductions in weight, blood pressure, uric acid, and weight circumference [3]. Similar cardiovascular benefits have been identified in studies with dapagliflozin (DECLARE TIMI-58 trials) and canagliflozin (CANVAS), however with regards to major adverse cardiovascular event (MACE), as defined by the United States Food and Drug Administration (US FDA) guidelines, there were no significant benefits over placebo for dapagliflozin [4], these findings are summarized in Table 1[5]. The CANVAS trial examined effects of canagliflozin where the treatment group had less events of the measured primary outcome (see Table 2), which was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke[6]. However, effects of individual components of the primary composite in the CANVAS trial were not as significant as when compared as a composite[6].

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Furthermore, there has been no evidence suggesting that there is an increased risk of hypoglycemic episodes when taking SGLT2i, unless taken in combination with other drugs such as sulfonylureas[1]. However, as with the challenges of any new drug, there are adverse effects that are not well understood and can therefore lead to delays in diagnosis and treatment with potentially life-threatening consequences in some patients. Due to the inherent mechanism of the drug, glycosuria is a side effect of the drug resulting in a potential increase in risk of urinary tract infections and genital mycotic infections [7]. Furthermore, of concern in the peri-operative period is the risk of euglycemic diabetic ketoacidosis[7].

Current SGLT2 usage in Australia

Agents covered by Pharmaceutical Benefits Scheme (PBS) include dapagliflozin, empagliflozin and ertugliflozin[8].

To assess usage of SGLT2i in Australia, monthly data regarding their prescriptions were extracted from the Pharmaceutical Benefits Australia website [9], via methods previously reported [10]. Pharmaceutical Benefits Scheme (PBS) codes for dapagliflozin, empagliflozin and ertugliflozin that were utilized can be seen in supplementary Table 1. Since their introduction, there has been a rapid increase in the use of SGLT2i in Australia, with monthly prescriptions increasing from 14 in December 2013 to 196, 975 in August 2019 (see Figure 1). The growing number of prescriptions highlight the importance of understanding the acute and long-term sequelae of this group of medications.

Urological implications

Lower Urinary Tract Voiding Dysfunction

Few studies regarding SGLT2i induced lower urinary tract symptoms (LUTS) have been published, however a retrospective case series study which included 50 patients from which full data was gathered, reports that pollakiuria and nocturia were the most prevalent LUTS, after initiation of SLGT2i, whereas other forms LUTS were pre-existing (see Table 3) [11]. The prevalence of new onset LUTS, in patients being treated with SGLT2i have may profound impact of quality of life, due to

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sleep disturbances [11]. As a result, there may be a theoretical risk of adverse effects related to volume depletion, including orthostatic hypotension and dizziness, which may precipitate falls [12]. Further, it has been identified that patients without autonomic neuropathy generally experienced a higher severity of symptoms [11], therefore in this population, benefits of continuing therapy with SGLT2i needs to be compared with the impacts on quality of life. It has also been reported that control of HbA1c levels was more efficient in patients in with autonomic neuropathy [11], therefore this subset of patients may be ideal for SGLT2i therapy. While no mechanistic theory has been suggested for these findings, it can be speculated that glycosuria induced osmotic diuresis may have role in pollakiuria and nocturia. However, another study conducted by Tanaka et al investigating the effects of canagliflozin and increased urine output found that the effects are probably due to natriuresis rather than glucosuria[13]. The increased urine output with this study was shown to be transient with a return to baseline on the second to fifth day of treatment, likely due to effects of canagliflozin increasing plasma renin activity and decreasing plasma ANP and NT-proBNP[13]. Therefore, more studies are required to quantify and assess the risk of developing LUTS due to treatment with SGLT2i.

Genital Infections

The risk of developing genital mycotic infections can be increased by up to 5 times in patients being treated with SGLT2i, with the risk of developing these infections increasing in the first month and enduring for the duration of the treatment[14]. Glycosuria resulting from diabetes likely provides a favourable substrate for growth of organisms and this effect is further enhanced by the pharmacologic glycosuria induced by SGLT2i[15]. A study which examined 173 cases of adverse drug reactions across 165 patients, reported an adverse drug reaction (ADR) rate of 47% for genital mycotic infections and 4% for urinary infections [16], clinical trials however have reported genital mycotic infection incidence rates of up to 6% [17]. This risk is further enhanced in uncircumcised men and those with poor genital hygiene [18]. Genital infections in males that have been associated with SGLT2i use, include balanitis, balanoposthitis, phimosis and paraphimosis [19]. Genital mycotic infections in males respond well to standard antifungal therapy (Table 4) [20] which can include clotrimazole 1% or miconazole 2% in combination with hydrocortisone 1% as a topical cream to be used twice daily till symptoms resolve [21]. If the patient does not tolerate topical creams or prefers oral medication, a single dose of oral 150mg fluconazole can be used [21].

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However, genital mycotic infections are inherently more common in women than in men [22]. Vulvovaginal candidiasis is of particular importance in women, as 75% of them will become symptomatic at least once in their life [22], and this risk is further enhanced in those with diabetes and medication with SGLT2i therapy [12]. Risk factors for developing genital mycotic infections in these patients include, topical corticosteroid use, pregnancy, estrogen therapy, oral contraceptives, and prior history of genital mycotic infections [12]. Genital mycotic infections in patients taking SGLT2i can be treated with standard antifungals [12]. Standard therapy for vulvovaginal candidiasis can involve 500mg clotrimazole as a single dose vaginal pessary, 200mg clotrimazole vaginal pessary or 2% topical cream for a duration of three days, or a six-day course of either 100mg clotrimazole as a vaginal pessary or a 1% topical cream [23]. If the patient prefers oral therapy or does not tolerate vaginal creams, a single day treatment of 150mg fluconazole may be used, provided the patient is not pregnant [23]. Nystatin may be considered, in patients who do not tolerate the other medications, however it is lower in efficacy and may result in treatment failure [23]. Uncommonly, patients treated with SGLT2i may grow Candida *glabrata* [12], where typical treatment can be ineffective, therefore it is recommended to use a two-week treatment of 600mg boric acid as a once daily vaginal pessary [23]. If non candida species are isolated, they usually respond well to non-fluconazole azole therapy, which is applied topically for seven days or more [22].

When choosing to commence a patient on SGLT2i, a careful history of relevant risk factors should be obtained which includes a history of prior infections, however risk of potential mycotic infections should not necessarily exclude a patient from trialing therapy [16]. Each patient should be given advice regarding personal hygiene, as studies have demonstrated that this leads to increased drug compliance and reduced risk of genital mycotic infections [24]. Fluid intake should also be encouraged, as the production of dilute urine can help reduce the risk of infections, unless the patient has volume overload related co-morbidities [25]. If the patient develops recurrent genital infections, then a decision to cease treatment is one that should be made together with the patient [16]. Usually these infections tend to be mild to moderate in nature and can be effectively treated by following standard practices [18], however cessation of the drug is warranted in the event of serious infections. A study which examined 691 patients with SGLT2i prescriptions showed that 2.5% of patients interrupted treatment due to recurrent genitourinary infections [26]. High HbA1c

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levels have not been shown to increase risk of developing genital infections in patients being treated with SGLT2i contrary to DPP4 inhibitors[27].

Fournier's Gangrene (FG) is a rare polymicrobial infection of the genital and perineal areas that has been associated with SGLT2i, that can be fatal when missed[28]. A post marketing case review showed that since the US FDA issued a warning in 2018 regarding the potential for SGLT2i to cause FG, there has been an increasing number of SGLT2i associated FG cases being reported[29]. It is possible the resulting increase in reports could be due to enhanced physician vigilance, that may have followed the US FDA warning [29]. A study which analysed data from the US FDA adverse events reporting system found the number of SGLT2i related FG cases reported rose from 103 in 2018 to 407 in 2019[30]. FG is a rapidly progressive necrotizing fasciitis that typically requires surgical debridement and antibiotic treatment[31]. Risk factors for developing FG include medical factors such as diabetes and immune suppression, renal failure, and liver failure, as well as lifestyle factors including smoking and alcohol consumption[31]. Presentation of FG can be quite variable, from mild cellulitis to severe pain with associated oedema and signs of systemic toxicity, therefore a high degree of suspicion is recommended when considering genital infections in patients on SGLT2i[31]. Other clinical findings associated with FG that may assist in making the diagnosis include tissue necrosis, crepitus, ecchymoses and bullae[31].

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Bacterial Urinary Tract Infections

The US FDA report in 2015 identified 19 cases of urosepsis, in patients being treated with SGLT2i, however studies show, SGLT2i as a class do not significantly raise the risk of UTI, when compared with placebo and active management with glitazones, incretins, metformin and sulfonylureas [32]. Clinical trials have reported incidence in UTI that vary from 4% to 9%, that range from mild to moderate intensity, while severe infections have been identified in up to 0.4% of patients [17]. It is theorized that while the effects of SGLT2i induced glycosuria creates an environment favouring

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organism growth, these effects may be counter-balanced by the resulting osmotic diuresis which improves urinary flow[33]. A large-scale study conducted by Dave et al, pooled data from two large American health insurance databases (IBM MarketScan and Clinformatics Datamart), to compare UTI risk with initiation of SGLT2i compared to DPP4 and GLP1 agonists[34] . Primary endpoints (severe UTI) for the study included primary UTI hospitalisations (urethritis, cystitis, and pyelonephritis), hospitalisations with pyelonephritis and hospitalisation with urosepsis[34]. Secondary endpoints for the study included UTI where outpatient antibiotic treatment was initiated and any UTI requiring hospitalisation[34]. Results after propensity matching showed that SGLT2i were not associated with an increased risk of UTI (as defined by the primary and secondary endpoints), when compared with initiation of DPP4 and GLP1 agonists[34]. Individual comparison of SGLT2i medications, however demonstrated that dapagliflozin may be associated with an increased risk of UTIs [32]. Studies have shown that through the recommended dosing ranges pharmacologically induced glycosuria plateaus for most SGLT2i except for dapagliflozin which continues to rise through the dosing range, which may explain the risk of increased UTI with dapagliflozin usage[32].

A case report suggests that caution may be advised when considering dapagliflozin in the setting of bladder outlet obstruction[35]. Therefore, practitioners should be aware of potential rare infections of the renal parenchyma requiring urological referral, such as xanthogranulomatous pyelonephritis and emphysematous pyelonephritis, which are associated with urinary tract obstruction, altered metabolic responses, and poorly treated urosepsis [36]. Further research is required to quantify the effects of SGLT2i on bladder outlet obstruction.

Xanthogranulomatous pyelonephritis is rare subtype of pyelonephritis that is characterized by destruction and replacement of the renal parenchyma with a granulomatous tissue mass that consists of macrophages containing lipids, which can present with flank pain and a palpable renal mass[36,37]. Other symptoms are non-specific and can include fever, weight loss and general malaise[37]. This disease usually occurs in the setting of chronic or recurrent UTIs and is typically associated with urinary tract obstruction[36]. Diagnosis requires CT imaging and the mainstay of treatment is usually a nephrectomy[37].

Emphysematous pyelonephritis is characterized as a necrotizing infection with associated free gas formation within the renal parenchyma that is usually associated with diabetes and

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obstruction[36,37]. Diagnosis can often be delayed as symptoms may be poorly differentiated from that of a classic UTI[37]. Investigation with CT scans will reveal the presence of gas in the renal parenchyma, where the radiological classification is defined by anatomical location of gas formation[37](Figure 2). Severe infections can progress to systemic shock, acute renal failure or DIC, all requiring urgent management[37]. Treatment usually includes percutaneous drainage or nephrectomy as well as systemic antibiotic therapy[37].

SGLT2i usage increases risk of asymptomatic bacteriuria, which is a strong risk factor for developing subsequent recurrent or severe clinical UTIs in patients with diabetes[38]. Therefore, caution is advised when prescribing SGLT2i in patients with significant background of co-existing risk factors for developing asymptomatic bacteriuria[38]. These include proteinuria, years lived with diabetes, poor HbA1c values, history of UTIs[38]. While it is unknown whether all cases of asymptomatic bacteriuria result in clinical UTI, current guidelines suggest routine screening and treatment with antibiotics is not recommended in diabetic patients due to risk of adverse effects of antibiotics and bacterial resistance[38]. Similarly asymptomatic pyuria should not be used as the only indicator for receiving antibiotic treatment as this can be present at baseline in many patients, therefore diagnosis and treatment should be guided by clinical symptoms[39].

It is advised that when, initiating an SLGT2i, practitioners should take note of previous history of UTIs and risk factors associated with complicated UTIs (obstruction, foreign body, incomplete voiding, vesicoureteral reflux, pregnancy, immunosuppression, UTIs in males, neurogenic bladder) [40], and consider choosing a non-dapagliflozin SGLT2i, if worried. There is no evidence currently to support routine monitoring of patients with urinalyses and urine m/c/s [41]. When uncomplicated UTIs are identified, standard therapies are sufficient for treatment [41], however should be guided by local resistance rates [42].

Peri-operative implications of SGLT2 inhibitors

Pertinently, the use of SGLT2i has also been associated with increased risk of developing euglycemic diabetic ketoacidosis, a medical emergency[43], with literature describing event rates of 0.1% (0.06% in control groups) [44]. Triggers include stressors such as surgery, fasting, and intercurrent illness, medication changes[45]. The presentation of typical diabetic ketoacidosis includes hyperglycemia with ketoacidosis, however patients taking SGLT2i can be euglycemic due

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to glycosuria, which can lead to a delay in diagnosis[43]. Ketoacidosis in the peri-operative period is precipitated by interplay between fasting state and surgical stress acting in tandem with the osmotic diuresis resulting from SGLT2i leading to loss of glucose and volume in the urine[46]. The loss of glucose in the urine results in decreased secretion of insulin and increased secretion of glucagon, whose production is further enhanced due to SGLT2 receptor blockade in the pancreatic alpha cells in islet of Langerhans that function as sensors for glucose, which interpret the block as hypoglycemia[46]. This increase in glucagon to insulin ratio results modifies the metabolic pathways of lipolysis, ketogenesis and free fatty acid oxidation leading to production of ketones[43,46]. Furthermore, there is impaired ketone clearance due to SGLT2i induced re-absorption of ketones from urine[46].

Time to presentation of euglycemic DKA can vary greatly depending on type of surgery involved, as patients who underwent bariatric surgery had presentations range from hours to weeks[45]. Therefore, due the variable nature of time to presentation, patients should be informed on symptoms of euglycemic DKA, and potentially have increased monitoring of blood ketones following surgery.

SGLT2i should be ceased 24 to 72 hours prior to major surgery [7], however there have been cases reported where patients still developed euglycemic DKA despite cessation 48 hours before [47]. Decision to cease SGLT2i may depend on the type of surgery involved and may only require withholding on the day for minor procedures occurring in day surgery, however this should be guided by surgical and anesthetic advice [45]. Prolonged cessation of SGLT2i of greater than 72 hours may be warranted in some patients, which would require a plan for glycemic control involving endocrinology, anaesthesiology, and the surgical team [45]. Practitioners should not rush to recommence SGLT2i immediately following surgery, as this can precipitate euglycemic DKA [48]. Instead the drugs should be recommenced when the patient feels well enough to tolerate oral food intake and is well hydrated [49]. Given there are patients who may be on metformin-SGLT2i combination drugs, cessation of one often means both, in these patients prolonged cessation of metformin can result in poor glycemic control, therefore separate prescriptions for metformin can be necessary in these patients [45].

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Recommendations

Caution is advised in patients with pre-existing risk factors for genital infections, such as topical corticosteroids use, pregnancy, estrogen therapy, oral contraceptives and uncircumcised males [18]. Patient education regarding potential infections and proper genital hygiene could be key for prevention or early detection[18]. Mild to moderate infections should be treated according to standard clinical guidelines [12,20,41].

Peri-operative counselling: per above guidelines. It is recommended that SGLT2i are ceased 48 hours prior to their surgery and resumed when safe, to minimize risk of developing euglycemic diabetic ketoacidosis [7,50,51]. If SGLT2i are not ceased and bloods show elevated blood ketones or high HbA1c, it is advised that non-urgent surgery be postponed[50]. Euglycemic diabetic ketoacidosis should be approached as a medical emergency and therefore peri-operative patients with elevated ketones require review by an endocrinologist or the on-call physician[50].

Conclusion

As SGLT2i are relatively novel, effective agents, further studies are required to clarify their adverse effects and potential complications. Mild to moderate genital infections and UTIs can be treated according to local guidelines, however severe infections require urgent referral[12,41]. Perioperatively euglycemic diabetic ketoacidosis is of most concern, requiring immediate diagnosis and management [7]. Regardless, a high degree of suspicion is advised with patients taking these medications, to ensure early diagnosis and treatment.

Conflicts of Interest

None of the contributing authors have any conflict of interest, including specific financial interests or relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

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Sodium Glucose-Linked Transport Protein 2 Inhibitors	SGLT2i
Type 2 Diabetes Mellitus	T2DM
Sodium Glucose-Linked Transport Protein 1 Inhibitors	SGLT1
Hospitalization due to heart failure	HHF
MACE	Major Adverse Cardiovascular Events

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m/c/s	Microscopy, culture & sensitivity
US FDA	United States Food and Drug Administration
PBS	Pharmaceutical Benefits Scheme
LUTS	Lower Urinary Tract Symptoms
Fournier's Gangrene	FG
UTI	Urinary Tract Infection
CT	Computed Tomography
DIC	Disseminated Intravascular Coagulation
DKA	Diabetic Ketoacidosis

Abbreviated words in manuscript

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Figure Legends

SGLT2 inhibitor prescriptions have seen a steady rise since introduction to the Australian market

Fig 1

Pharmaceutical Benefits Schedule data was acquired from the website utilising the relevant codes (including combination drugs) as seen in Table 2 for Empagliflozin, Dapagliflozin and Ertugliflozin prescriptions since first recorded usage up until mid late 2019. The data was plotted to a line graph as number of prescriptions per month. As listed in the figure the gray line corresponds to dapagliflozin, the yellow to empagliflozin and the blue line to ertugliflozin. Dapagliflozin and empagliflozin have seen significant rise in usage, compared to ertugliflozin since approval.

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CT Scan of a patient with Acute Emphysematous Pyelonephritis

Fig 2

Axial abdominal CT scan of a patient with diagnosed emphysematous pyelonephritis, provided as a reference figure.

Supporting Information

PBS codes for Dapagliflozin, Empagliflozin and Ertugliflozin

Supplemental Table 1

Table comprising of pharmaceutical benefits schedule codes (Australia) that were utilised to determine sodium glucose-linked transport protein 2 inhibitor usage in Australia since apparent first usage up until mid late 2019.

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Table 1: Summary of Relative Risk Reductions from Class effects of SGLT2 inhibitors on cardiorenal outcomes by Kluger et al [5].

Outcome	EMPA-REG (Empagliflozin)	DECLARE TIMI-58 (Dapagliflozin)	CANVAS (Canagliflozin)
Hospitalisation due to heart failure	35%	27%	33%
Hospitalisation due to heart failure or CV death	34%	17%	22%
MACE	14%	7%	14%

† CV death – Cardiovascular Death

‡ MACE – Major adverse cardiovascular event – defined according to American Food and Drugs Administration

Table 2: Summary of Event Rates (per 1000 patient years) from the CANVAS Program on the Primary Outcomes [6].

Outcome	Canagliflozin	Control
Death from Cardiovascular Causes	11.6	12.8
Nonfatal Myocardial Infarction	9.7	11.6
Nonfatal Stroke	7.1	8.4
Composite	26.9	31.5

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Table 3: Summary of findings from Lower urinary tract symptoms (LUTS) in males with type 2 diabetes recently treated with SGLT2 inhibitors—overlooked and overwhelming? A retrospective case series [11].

New Onset LUTS Prevalence	Patients with Autonomic Neuropathy	Patients without Autonomic Neuropathy
Pollakiuria	43.8%	73.6%
Nocturia	25%	50.0%
HbA1c at approximately 4.5months	7.2%	7.8%

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Table 4: Examples of standard therapy for genital mycotic infections in males and females [20, 21, 23].

Sex	Indication	Medication	Duration
Male	Standard Antifungal Therapy	Topical Creams: Clotrimazole 1% OR Miconazole 2% PLUS Hydrocortisone 1%	Twice Daily until symptoms resolve
	Intolerance of topical therapy or preference for oral therapy	Fluconazole 150mg (oral tablet)	Single Dose
Female	Vulvovaginal Candidiasis	Clotrimazole 500mg (vaginal pessary)	Single dose vaginal pessary
		Clotrimazole 200mg (vaginal pessary) OR Clotrimazole 2% (topical cream)	Three Days

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		Clotrimazole 100mg (vaginal pessary) OR Clotrimazole 1% (topical cream)	Six Days
	If oral therapy preferred AND Not pregnant	Fluconazole 150mg (oral tablet)	Single dose
	Candida Glabrata	Boric Acid 600mg (vaginal pessary)	Once daily for 14 days

Table 5: Several pertinent recommendations by ANZCA regarding SGLT2 Inhibitor use peri-operatively[50] include:

SGLT2i be ceased up to 3 days pre-operatively or in other physically stressful situations (the two days prior to surgery and the day of surgery). This may require an increase in other glucose lowering agents during this time.
Strongly consider postponing non-urgent surgery if SGLT2 inhibitors have not been ceased 3 days prior to surgery, and blood ketones are >0.6, or where HbA1c is >9.0%, as these are indicators of insulin insufficiency, and a high risk of DKA.
Routinely check both blood glucose and blood ketone levels in the perioperative period if the patient is unwell or is fasting or has limited oral intake and has been on a SGLT2i prior to surgery.

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Euglycemic diabetic ketoacidosis should be treated as a medical emergency.
Patients who have day surgery/procedures should only recommence SGLT2i if on full oral intake. It may be prudent to consider delaying recommencement of SGLT2i for a further 24 hours though consideration should also be given to the effects of withholding SGLT2 inhibitors (and metformin if on combined medication) on glycaemic control.
For more major procedures, SGLT2i should only be restart post-operatively when the patient is eating and drinking and close to discharge (usually 3-5 days post-surgery).

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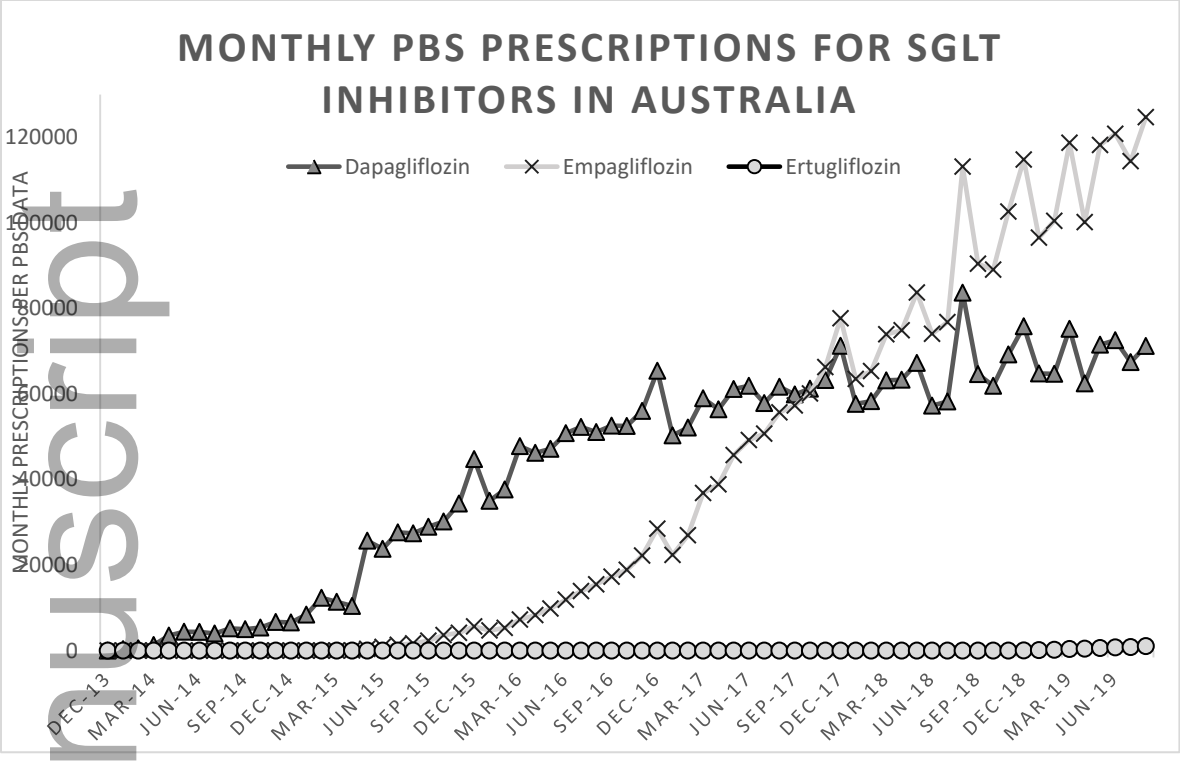

Figure 1: Monthly prescription for SGLT2 inhibitors in Australia per PBS data

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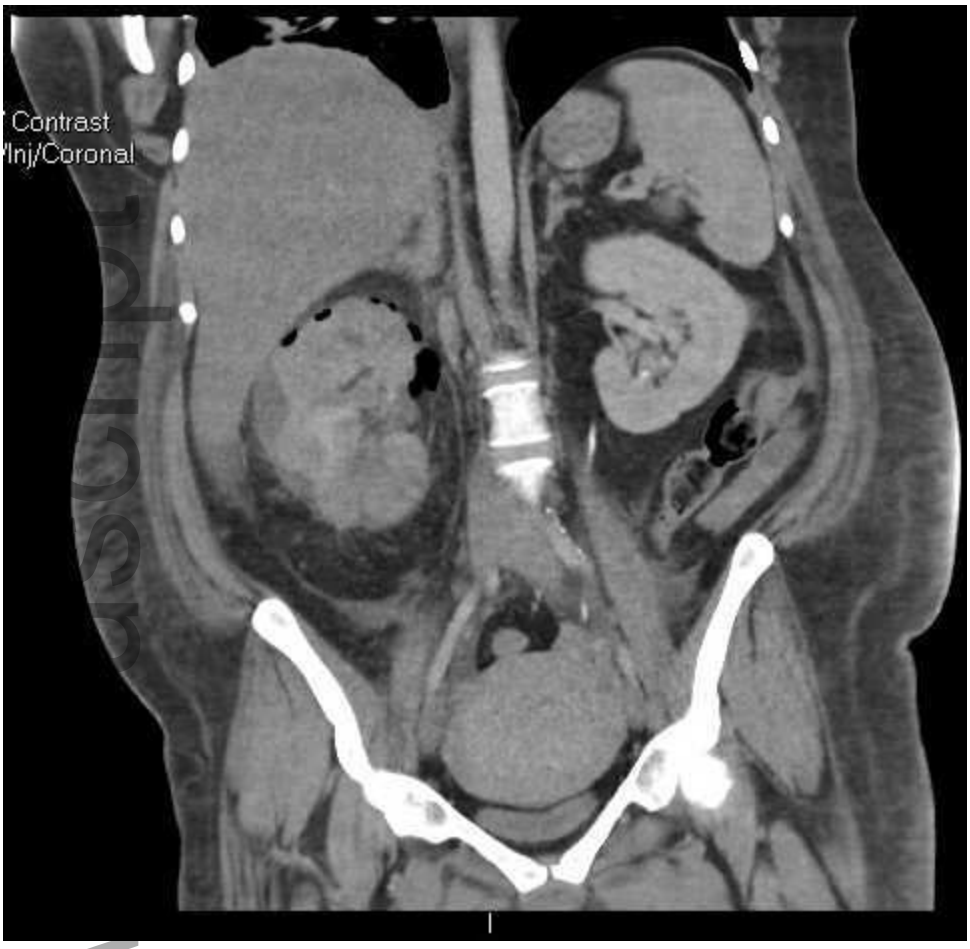

Figure 2: Coronal CT Abdomen Pelvis with IV Contrast in a Patient with Emphysematous Pyelonephritis

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