COST OF PYELONEPHRITIS IN TYPE- 2 DIABETES (COPID STUDY) - A COST OF ILLNESS STUDY

A dissertation submitted in partial fulfillment of the rules and regulations for MD General Medicine examination of the Tamil Nadu Dr.M.G.R Medical University, Chennai, to be held in May 2018

DECLARATION

This is to declare that this dissertation titled ― Cost of Pyelonephritis in type- 2 Diabetes Mellitus (COPID study)- A cost of illness study is my original work done in partial fulfilment of rules and regulations for MD General Medicine examination of the Tamil Nadu Dr.M.G.R Medical University, Chennai to be held in May 2018.

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CERTIFICATE I

This is to certify that the dissertation entitled –—Cost of Pyelonephritis in type- 2 Diabetes Mellitus (COPID study) - A cost of illness studyis a bonafide work done by Dr. Ebenezer Daniel towards the partial fulfilment of rules and regulations for MD General Medicine degree examination of the Tamil Nadu Dr.M.G.R Medical University, to be conducted in May 2017.

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CERTIFICATE II

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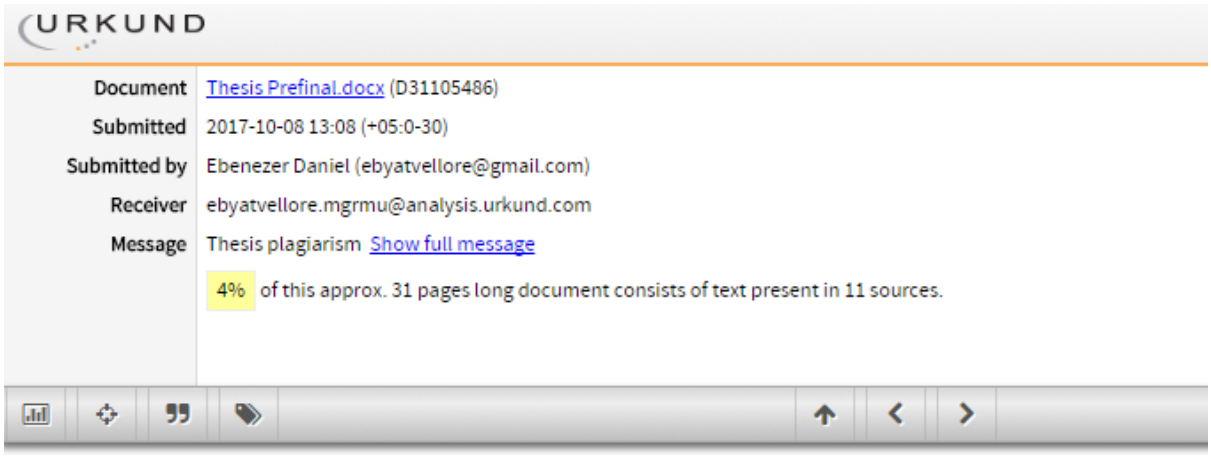

This is to certify that this dissertation work titled “Cost of Pyelonephritis in Type-2 Diabetes (COPID Study) - A cost of illness study” of the candidate Dr. Ebenezer Daniel with registration Number 201511455 in the branch of General Medicine has been submitted for verification. I personally verified the urkund.com website for the purpose of plagiarism Check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows 4% percentage of plagiarism in the dissertation.

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Cost of Pyelonephritis in Type- 2 Diabetes (COPID study) - A cost of illness study

INTRODUCTION

Diabetes Mellitus poses a great economic burden to the family. One of the important causes of a hospital admission of the diabetic patient is acute Pyelonephritis. The management includes empiric antimicrobial therapy based on local susceptibility pattern, isolation of the organism followed by pathogen directed therapy. With the rise in the incidence of Extended spectrum beta lactamase producing organisms, the cost of care has significantly increased. Besides this diabetes predisposes the patient to develop complications of Pyelonephritis which also increase the cost.

There is a need to quantify this burden in the Indian setting. Besides this, the indirect and intangible costs which are often overlooked also contributes significantly to the cost of care.

HYPOTHESIS

Our hypothesis was that Diabetic patients would have a higher cost than non-Diabetic patients during their admission with a poorer quality of life.

AIM

To estimate the cost of Acute Pyelonephritis in patients with Type 2 Diabetes mellitus admitted in general medical wards

OBJECTIVES

1. To estimate the total cost of a single admission for Acute Pyelonephritis
2. To estimate the difference in cost of admission for Acute Pyelonephritis between Diabetics and Non-Diabetics
3. To find the difference of cost of admission for Acute Pyelonephritis caused by ESBL organisms and non-ESBL organisms

LITERATURE REVEIW

Global economic burden of Diabetes

Diabetes causes substantial economic burden globally. A recent cost of illness study estimated global cost of diabetes with data from 184 countries including low and middle income countries. The global cost in 2015 based on the study was around US$ 1.31 trillion or 1.8-1.9 of global gross domestic product (GDP). (1) The indirect costs also contributed significantly to the cost of care (around 34.7%). The labour force drop out (48.5%) and mortality (45.5%) contributed to the indirect costs majorly followed by absenteeism. In the low income and middle income countries analysis of 86 cost of illness studies from 2001 to 2014 estimated annual direct costs ranging from INT$ 242 to $4129. (2)

Table 1 Global Economic burden of Diabetes in 2015. Adapted from Bommer et al(1)

Region	Indirect costs	Percentage of GDP
Sub-saharan Africa	19.45 (44%)	1.2%
East Asia and Pacific	318.89 (38.2%)	1.6%
Europe and Central Asia	276.31 (30.8%)	1.4%
Latin America and the Caribbean	129.89 (21.9%)	2.4%
Middle East and North Africa	41.97 (35.1%)	1.3%
North America	499.40 (36.3%)	2.6%
South Asia	25.86 (57.4%)	1.0%

Health care in India

Health care in India is primarily from the private medical sector. 70% of the urban and 63% of rural India gain access to health though the private sector. However only 28.7% of the households (urban 28.2%, rural 29%) have any member covered by a health scheme or insurance(3). The public sector has national programmes to cover for HIV, Tuberculosis and Leprosy. But such a system is not existential for Diabetes and its complications. Around 8.0% men and 5.8% women have diabetes in India (3). A report by the health care access initiatives by a pharmaceutical company exposed that nearly 63 million are in debt and a third of them are pushed below the poverty line due to health care expenditure(4). Hence to understand the burden of disease in regards to the economy, cost analytical studies are needed.

Diabetes in India

Diabetes is a major contributor to morbidity and mortality in both infectious and non-communicable diseases. The International Diabetes Federation has ranked India only next to China with about 69.2 million people (56.2- 133.4 million) with Diabetes in 2015(5). The proportional mortality due to Diabetes is 2% based on WHO Non communicable diseases country profile (2014) which accounts to 1. 96 million deaths(6).

By the thrifty genotype theory by which the genetic material are adapted to the environment, Indians are programmed to a low calorie diet. With the sudden increase in lifestyle and diet, the body is unable to tolerate the high calorie intake predisposing them to diabetes(7). The process starts even before birth when the insulin resistance develops. This happens as the muscle of the foetus becomes resistant to insulin while developing in the uterus. Based on the New Delhi birth cohort, it has been noted that those who gain weight not necessarily the obese are more predisposed to developing Diabetes (8). Hence the Indian genotype need not be obese to develop Diabetes.

Cost of Diabetes in India

India is a growing economy. The GDP in 2073.54 billion $US (Rs.1,35,796.13 billion) and estimated annual wages are 1203.54 $US (Rs.78,819.83). Diabetes in India a growing epidemic. Because of the chronic nature of the illness, the costs incurred lays a huge burden. The prevalence of Diabetes Mellitus among the age group 20-79 based on the IDF data is 8.7% (7.0-10.6%). The total cost of Diabetes Mellitus in percent of GDP is 1.04 (0.87- 1.25). Of this the direct costs account to 0.46% (0.39- 0.56%). (1) Direct costs in percent of total health expenditure is around 9.18 (7.67-11.07) amounting to 9.58 million $US (Rs.627.39 million). Direct costs per patient was 138.52 $US (Rs.9071.67). A low income Indian family would roughly spend around 25% of the total family income to diabetic care. It has been found that the largest single expenditure for Diabetes care in India is inpatient hospital admission (9).

Table 2 Distribution of Indirect costs due to diabetes in India (1)

Absenteeism	**Labour force drop out**	**Mortality**	**Presenteeism**
0.02 (0.02-0.03)	0.11 (0.09-0.13)	0.44 (0.37-0.52)	0.01 (0.01-0.01)

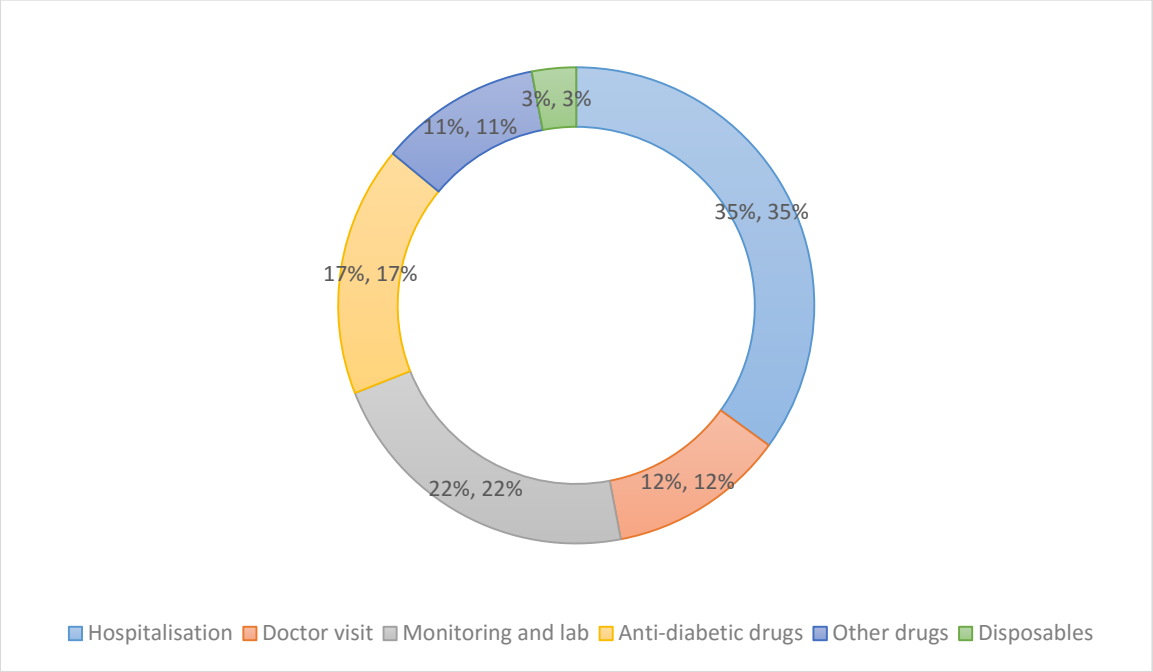
Comparing the global data the indirect costs due to mortality seems to contributing majorly to the indirect costs.

The total annual expenditure for diabetes is around US $227 (10000 INR) in urban areas and US $142 (6260 INR) in the rural areas. Low-income groups spend a higher proportion of their income on diabetes care (34% in urban low socio economic status versus 27% rural low socioeconomic status). The medical costs in a patient with diabetes multiple two to fivefold higher than those without diabetes(10). The problem is a vicious cycle when the diabetes is uncontrolled because of cost issues leading to more complications which further increases the cost.

Indian studies have shown that the comorbidities and complications in diabetes are more in the lower socio economic group. (11). They have also showed that since the lower socio economic group sought health care later, they had more complications. There was a difference of 7 years in the age of diagnosis between the economic groups. The costs subsequently will increase since the diabetes would be uncontrolled and complications could have set it. This is a classic example of the link between health and poverty where the poor are driven below the poverty line when a major complication occurs. (11).

It is appropriate to look at the landmark economic studies done in diabetes in India. The CODI (Cost of Diabetes in India) was a community based study done to survey the cost of Diabetes in India(12). It was preceded by the Bangalore Urban district study (BUD study) which is a pilot study. The results showed that 65% of the costs were ambulatory care and 35% was due to hospitalisations. Though the therapy amounted 31% the specific anti-diabetic drugs was only 17%.

Figure 1 Direct costs in Diabetic care (Adapted from Kapur et al)(12)



Hospitalisation increases the cost of care. Cardiac complications were the most common and the costliest cause of hospitalisation followed by a non-healing wound(12). The overall cost of hospitalisation was around $US 200 (Rs.13,098). The hospitalisation for a Type 1 diabetic the cost was $US 120 (Rs.7,858.80) when compared to a type 2 diabetic which was $US 206 (Rs.13,490.94). When there were no complications the cost was $US 154 (Rs.10,085.46) however when there were more than 3 complications the costs increased to $US 259 (Rs.16,961.91).

Majority (89%) of the people used their household income to fund the treatment of Diabetes. Few others utilised government hospitals which are free. 22% of the elderly and 19% of the low socioeconomic group used their savings. When hospitalised he percentage of people who spent from their savings increased to 34%. 9-10% obtained loans from the employers and only 1 percent had insurance.

Socioeconomic status and health-care

The socio-economic status of an individual has important implications in health and health care. A low socio-economic status curtails access to proper nutrition and health care. In fact, a multicohort study and meta-analysis of 1.7 million people has shown that low socio-economic status was an independent and modifiable risk factor of mortality. (13) This risk is comparable to the risks posed by diabetes, hypertension and smoking.

In India, 73.37% of the households live in the villages. (14) 74.52 % of the people have a monthly income of the highest earning household member less than Rs.5000 (76 $US). 35.73 % of the rural population and 27.2% of the urban population are illiterate. The main source of income in 30.10% of the rural population is cultivation and 51.18% is casual labour. (14) Hence a significant population belong to the low socio-economic group. When assessing the economic burden, it is important to project background socio-economic status of the patient in perspective.

The socio-economic status has been historically divided into high, middle and low. It depends on the education, occupation and family income. There are many scales available to quantitatively measure the socio-economic status. These have to be individualised to each community. In 1976, the Kuppusamy scale was devised which is a composite score of education, occupation and monthly family income.(15) The family income in this scale is updated every year.

Table 3 The modified Kuppusamy scale

Education	Score
Profession or honours	7
Graduate or Post-graduate	6
Intermediate or Post-high school diploma	5
High school certificate	4
Middle school certificate	3
Primary school certificate	2
Illiterate	1
Occupation	**Score**
Professional	10
Semi-professional	6
Clerical, Shop-owner, Farmer	5
Skilled worker	4
Semi-skilled worker	3
Unskilled worker	2
Unemployed	1

Family income (1976)	Family Income (2014)	Family Income (2017)	Score
>2000	>36997	>41430	12
1000-1999	18498-36996	20715-41429	10
750-999	13874- 18497	15536-20714	6
500-749	9249-13873	10357-15535	4
300-499	5547-9248	6214-10356	3
101-299	1866-5546	2092-6213	2
<100	<1865	< 2091	1

Socioeconomic Class	Score
Upper class	26-29
Upper middle class	16-25
Lower middle class	11-15
Upper lower class	5-12
Lower class	<5

Adapted from Oberai et al (15) *Tulika singh et al* (16)

There is also disparity in health care between the socio-economic groups. It varies among different countries. (17) In each country there are unique challenges to bridge the gap between the socio-economic groups in regards to health care. In India, with the surge of the non-communicable diseases even in the villages and the shift of the health care from the public sector to the private sector, many people in the low socioeconomic group are pushed below poverty line.

PYELONEPHRITIS

Pyelonephritis is the infection of the upper urinary tract involving the kidneys, upper ureter, tissue surrounding the retroperitoneal space or perinephric space with clinical features of high grade fever with flank pain and laboratory evidence of pyuria with urine and/or blood growing the uro-pathogenic organism (18). Fever can be absent during the initial stage of the illness. Flank pain and renal angle tenderness is almost always present and its absence suggests an alternate diagnosis. A positive urinalysis confirms a urinary tract infection. Urine culture and blood culture guides antibiotic therapy in view of the high rates of community acquired resistant uropathogens. In view of the frequency and severity of the disease, accurate diagnosis, decision on antimicrobial therapy based on local susceptibility data and expert guidelines is paramount in the appropriate management.

Epidemiology

Urinary tract infections are more common in women. The overall estimated incidence rate is 18 per 1000 per year. The majority are community acquired (57.4%), 35.6% are hospital acquired and 7% are nosocomial. An estimated 1 in 3 women will have a minimum of 1 UTI diagnosed by a physician by the age of 24 and 40-50% will have at least 1 Urinary tract infection during their lifetime. Pyelonephritis accounts to 15-20% of patients with community acquired bacteraemia and sepsis and 35% in a hospital setting(19). A population based analysis of 3236 cases of pyelonephritis showed annual rates of 12-13 outpatient cases per 10,000 population and 3-4 inpatient cases per 10,000 population among women and 2-3 outpatient cases per 10,000 population and 1-2 inpatient cases per 10,000 population among men (20).

Diabetic patients have a 2-4 fold increase in bacteriuria compared to non-diabetic patients increasing the chances of an ascending infection (21). It has been shown that women with diabetes are 6-24 times more likely to have hospitalisation for pyelonephritis and males with diabetes are 3-17 times more likely than non-diabetic males (22).

Aetiology of pyelonephritis

The uropathogens are predominantly gram negative bacteriae. It is well established that Escherichia coli is the most common organism causing pyelonephritis. The pathogens differ based on age, presence of diabetes, structural abnormalities, spinal cord injury or indwelling catheters. However in all sub categories, Escherichia coli still is the most common organism. It is followed by Klebsiella pneumoniae, Staphylococcus saprophyticus, Enterococcus faecalis, group B Streptococcus (GBS),Proteus mirabilis, Pseudomonas aeroginosa, Staphylococcus aureus and candida species in the order of prevelance (23). Less virulent organisms that rarely cause infection in a normal intact urinary tract can cause serious illness otherwise(24). There has been an increase in Candida species, Enterococcus species as causative organisms (25). In Diabetic patients E-coli is again the most common cause (56.1%) (26). Klebsiella and Group-B streptococci have been found to be 2-3 times more common (27).

Figure 2 Epidemiology of Urinary tract infections in Uncomplicated urinary tract infections. Adapted from Flores-Mirales et al (23)

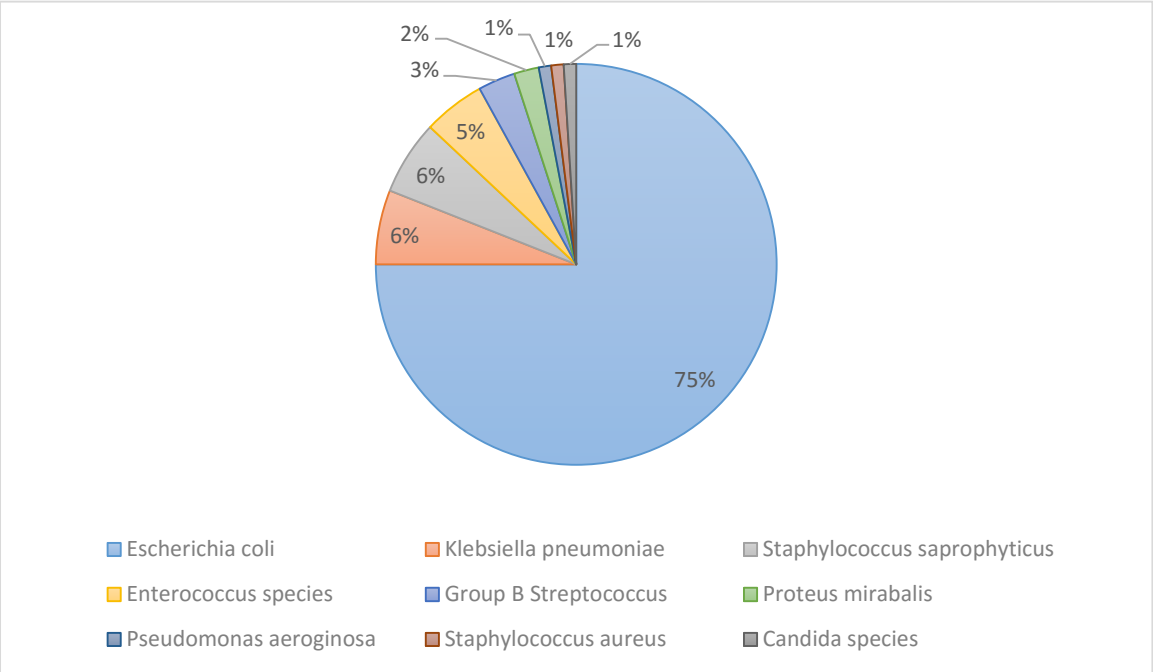
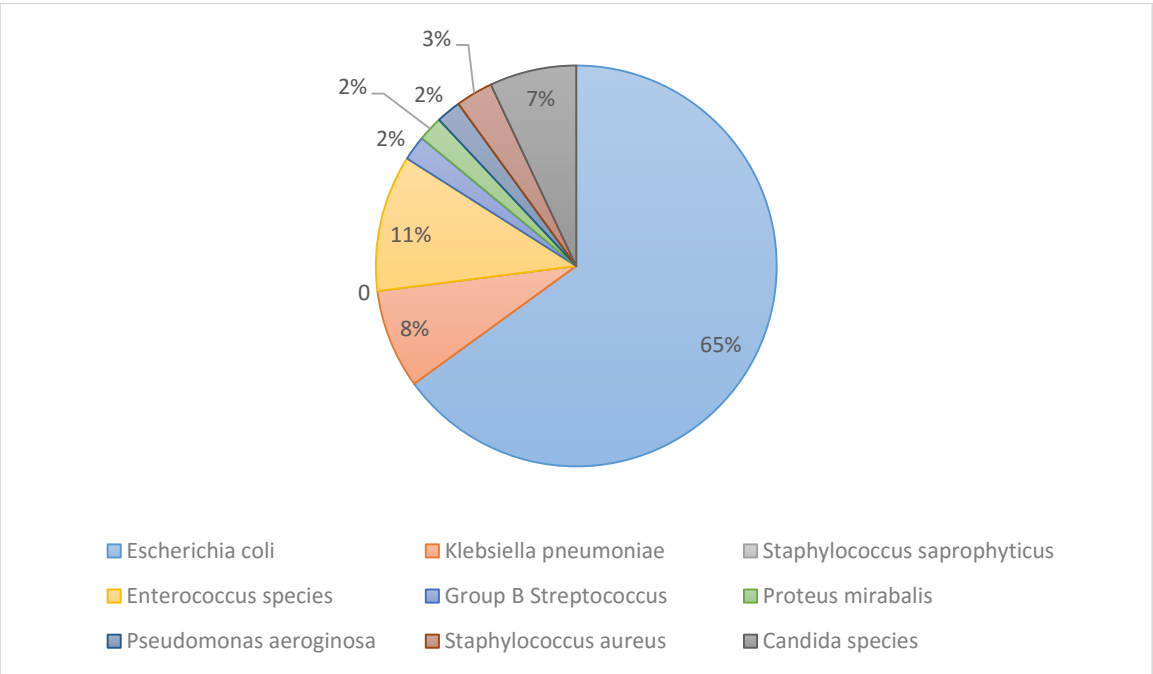


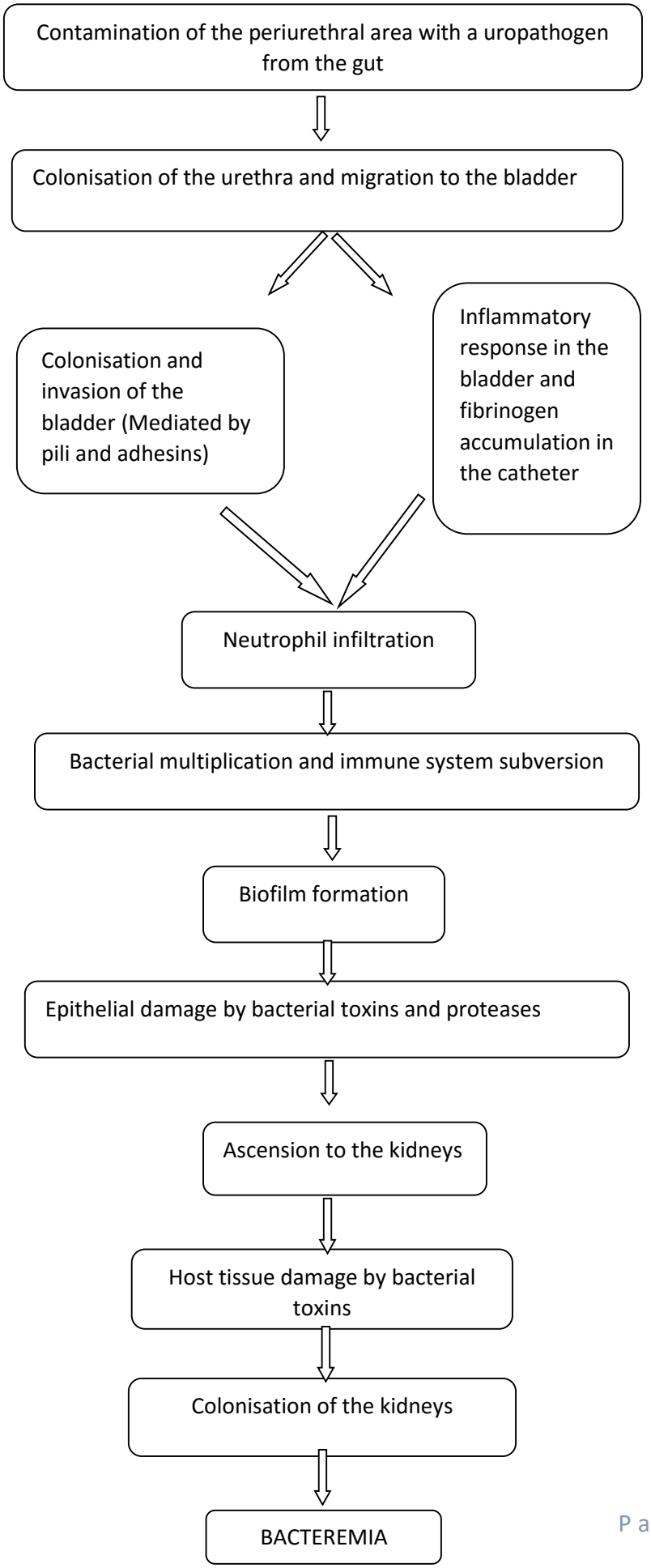
Figure 3 Epidemiology of Urinary tract infections in complicated urinary tract infections. Adapted from Flores-Mirales et al (23)



The urinary tract is sterile except for the distal third which contains commensal flora. This is protective to ascending infections. Individual susceptibility to urinary tract infections depends on genetic, biologic and behavioural factors (Table 1)(28). Each species has unique mechanisms that aid in colonisation and invasion which are determined by specific bacterial adhesive characteristics, the receptor repertoire on the epithelial surface and the surrounding fluids. An important step in the pathogenesis involves the colonisation of the urothelium with E-coli. More than 75% of the infections are due to progression of this ascending infection. The bacteria can directly invade the renal parenchyma from medulla to cortex. The local vascular channels in the kidney facilitate the spread/ transport of infection. This leads to development of abscesses within the renal parenchyma that can further rupture into the peri-nephric space. This space contains peri-nephric fat and the adrenal glands which are in turn surrounded by Gerota's fascia. When the abscess ruptures into this fascia it can track down anteriorly through the psoas/ transversalis fascia, superiorly into the sub-diaphragmatic space and inferiorly into the pelvis. Presence of urolithiasis is an important predisposing factor for development of Pyelonephritis.

Risk factors for development of recurrent urinary tract infection in young women include recent (<1 month) intercourse, spermicide use (12 months), new sexual partner,age of first urinary tract infection (≤ 15 years) and urinary tract infection in the mother. When an antibiotic is used for a urinary tract infection, there is collateral damage resulting in alteration of the commensals in the vagina increasing the risk of colonisation by multi drug resistant pathogens. (29)

Figure 4 Pathogenesis of urinary tract infections



Virulence factors associated with Pyelonephritis

Uropathogenic virulence factors are less frequently found in the commensal strains of fecal E-coli but seen in uropathogenic E-coli. P fimbriae are implicated in the pathogenesis because they mediate Gal-Gal- specific bacterial adherence to epithelial cells in the urinary tract. This permits bacterial colonization and stimulates inflammation. In patients who are immunocompromised the requirement for p fimbriae in initiating infection is reduced. Type-1 fimbriae is seen in uropathogenic and commensal E-coli. It is essential for colonisation, invasion and persistence. The adherence of E-coli with type-1 fimbriae to host cells in the urinary tract may promote the development of cystitis. The serological diversity of P fimbriae and the limited impact of anti-fimbrial antibodies complicate efforts to develop anti-p fimbrial vaccines (30). Bacterial internalisation is mediated by type 1 pilus adhesin, FimH. It also helps in invasion through interaction with α3ß3 integrin.

Table 4 Virulence factors used by main uropathogens. Adapted from Flores-Mirales et al (23)

Pathogens	Virulence factors				
	Adherence	Toxin	Immune evasion	Iron acquisition	Other
UPEC	F1C pili P pili S pili Type 1 pili Dr adhesins	HlyA CNF-11	HlyA Capsular antigens Yersiniabactin CNF-1		Antigen43 Flagella
Klebsiella pneumonia	Type 1 pili Type 3 pili		Capsule	Enterobactin Aerobactin	
Proteus mirabilis	NAFs PMFs AipAadhesins Taap adhesion	Haemolysis (HlyA and HpmA) Pta	ZapA Capsule	Yersiniabactin Proteobactin	Urease Flagella
Pseudomonas aeroginosa	Extracellular DNA Exopolysaccharides (alginate, PEL, PSL)	-	Capsule Elastase ExoS Phospholipase Rhamnolipids	Pyochelin Pyoverdin	Quorum sensing
Staphylococcus saprophyticus	Aas adhesion Sdrl adhesin Uaf adhesin	Aas	-	-	Urease
Enterococcus faecalis	Ebp pili Ace adhesin Esp adhesin	-	Epa	-	Sortage A Sig V Msr A and MsrB
Enterococcus faecium	Ebp pili Esp Adhesin	-	-	-	-

E-coli uses iron for synthesising DNA , electron transport and metabolising peroxides. In infection, as a part of self-defence the host limits the amount of iron to the uropathogenic E-coli. However, the E-coli have developed iron chelating mechanisms to combat this. Among them, the hydroxamatesiderophoreaerobactin is the most effective. It promotes growth of the bacteria even in limiting iron concentrations (31). Hemolysin is the cytolytic protein toxin secreted by uropathogenic E-coli. The most common one being α-hemolysin(32). It is seen with the severe forms of infections. It includes the release of iron from erythrocytes by lysis, disruption of phagocyte function and direct toxicity to host tissues.

Capsular polysaccharides are linear polymers of repeating carbohydrate units that include a prominent amino acid or lipid component. They coat the cell and interfere with O-antigen detection. The uropathogenic E-coli have group-II capsular Polysaccharides. They aggregate spontaneously because of a phosphatidic acid group. Among them, in particular the K1 capsule contribute to virulence by shielding the bacteria from phagocytosis and blocks the complement activating pathway (33). Limited number of capsular types account for most of the uropathogenic E-coli.

Colonisation of the renal parenchyma is by the expression of pyelonephritis associated pili (P). It binds to globoside containing glycolipids in the renal tissue. PapG, the P pilus adhesin interacts with TLR4 reducing the expression of polymeric immunoglobulin receptor (PIGR) causing impaired IgA transport across the epithelium. This prevents opsonisation and clearance. (34)

Three new candidate genes have been reported to be putative uropathogenic virulence genes- usp, iha and $iroN_{E.coli}$. The 'usp gene' is a homologue of the Vibrio choleraezot (zonulaoccludens toxin) gene found in uropathogenic E-coli using a DNA probe. In a study done in Japan, *usp* gene was observed in 24% of 50 stool samples with *E. coli* from healthy individuals, 80% of 195 cystitis isolates, and 93% of 76 pyelonephritis isolates (35). 'iha gene' was originally isolated from the E-coli O157:H7 strain as a part of tellurite resistance associated with PAI (Pathogenicity associated island) and is similar to the *V. cholerae* iron-regulated gene A (36). In a study done among 67 isolates of E-coli causing urosepsis, the prevalence of iha was found to be 55% (37). $iroN_{E.coli}$was originally identified in UPEC strain CP9. It is 77% homologous to a catecholesiderophore receptor gene observed in *Salmonella enterica. It* occurred in 57% of 14 faecal isolates without the known virulence genes *pap, hly*, or *cnf1*. *It was also seen* in 95% of 20 first-UTI isolates, and in 93% of 15 recurrent-UTI isolates. (38) Of these genes, i$roN_{E.\ coli}$ has been found to be strongly associated with UTI pathogenesis and *usp* plays a role in pyelonephritis and colonization of the peri-urethral area. The association of usp and iha are weaker in comparison to i$roN_{E.\ coli}$(39)

Immune response by the body to uropathogenic organism

As the uropathogen invades the bladder epithelial cells, Toll like receptor- 4 (TLR-4) recognises the organism and increases the cyclic AMP (cAMP) levels intracellularly. This leads to exocytosis of the pathogen and expulsion of the pathogen through the urine. If this step is overcome by the pathogen, they undergo autophagy into the lysosomes. The pathogens cause the lysosomes lose their degradative capacity. This is sensed by the lysosomal transient receptor potential mucolipin 3 channel (TRPML3). This causes lysosomal exocytosis leading to expulsion of the pathogen. Besides this the bladder epithelial cells also secrete cathelicidin and ß- defensin-1 which are anti-microbial peptides. They also secrete anti-microbial proteins like pentraxin 3 (PTX 3) and chemokines like CCR5 and CXCL-1. The pathogens also cause caspase-3 and caspase- 8 mediated apoptosis of the infected bladder epithelial cells. Apart from these, the mast cells, natural killer (NK) cells and macrophages secrete chemokines which attract neutrophils and other cells of the innate immunity to clear the pathogen. (40)

Biofilm formation

The pathogens evade the innate immunity by the invasion of the bladder epithelial cells. There is replication inside the epithelial cells which serve as bacterial reservoirs. Each reservoir has 4-10 non replicating bacteria which can remain latent for months. This can go on for several months before the development of significant bacteruria. These appear as numerous protrusion on the surface of urinary bladder termed as pods. On examining under scanning electron microscope, the luminal surface of the pods are smooth compared to the ruffled surface of the normal bladder epithelium. The pods visualised under the transmission electron microscopy (TEM) show bacteria embedded in a fibrous matrix in the cytoplasm. There is a halo around the bacteriae separating from the cell contents and each other. The matrix and the fibres expressed by the bacteria are intertwined providing a scaffold of support to the pathogen. This is the biofilm formed by uropathogenic organisms inside the bladder epithelial cells. This confers resistance to the organisms to antibiotics and host defences. (41)

Pyelonephritis in Diabetics

Diabetes causes predisposition to infections by a variety of mechanisms. It results in abnormalities in the immunological defence mechanisms like impaired migration, intracellular killing, chemotaxis and phagocytosis in leucocytes(42). The humoral activity appears to be normal as evidenced by normal response to vaccines. In regards to increased cause of urinary tract infections, it can lead to autonomic neuropathy causing diabetic cystopathy. This is leads to detrusor areflexia when there is damage to the efferent parasympathetic fibres. This causes incomplete bladder voiding, increased post-voidal residue, decreased peak urinary flow rate, bladder overdistention, and urinary retention(43). This may lead to proliferation of bacteria in the post residual collection of urine leading to increase incidence of urinary tract infectios. Glucosuria also leads to serve as a culture medium for uropathogens.

Further, recurrence rates are 25-42% in Diabetic patients which are significantly higher than patients without Diabetes. Incidence of Emphysematous Pyelonephritis is higher in patients with Diabetes. This is attributed to high levels of glucose, presence of gas forming organisms, impaired vascular blood supple, reduced host immunity, and presence of obstruction in the urinary tract favouring anaerobic metabolism. Gram negative facultative anaerobic organisms like Escherichia Coli are responsible for fermenting glucose and lactate producing gas. Carbon dioxide and hydrogen have been found to be the principal constituents. Gas may extend beyond the site of inflammation to the sub-capsular, perinephric and pararenal spaces. In some cases, gas was found to

be extending into the scrotal sac and spermatic cord. Pathological examination of the kidney reveals features of abscess formation, foci of micro- and macro-infarctions, vascular thrombosis, numerous gas-filled spaces and areas of necrosis surrounded by acute and chronic inflammatory cells implying septic infarction

Further, Diabetes predisposes to complications like Emphysematous cystitis, xanthogranulomatous pyelonephritis, intrarenal abscess, acute focal bacterial nephritis, acute multifocal bacterial nephritis, renal cortical abscess, renal cortico-medullary abscess, prostatic abscesses, perinephric abscess and renal papillary necrosis.

Imaging in Pyelonephritis

Imaging is not necessary to diagnose simple pyelonephritis. As recommended by the ACR appropriateness criteria, imaging is required only in 5% of the patients who do not demonstrate clinical improvement within 72 hours. (44) Imaging should also be used in patients who have increased predilection for disease progression, diabetic, pregnant, elderly, immunocompromised, have history of urolithiasis or structural abnormalities. The purpose of imaging is to rule out an obstructing calculi, complications like formation of an abscess and identify rare causes of renal structural abnormalities. (45) The recommended CT protocol for complicated urinary tract infection is a non-contrast examination (to assess for stone disease) followed by an enhanced phase at 90 to 120 seconds when there is uniform nephrographic phase enhancement of the renal parenchyma. CT findings of pyelonephritis include a persistent and/or striated nephrogram, thickening and mucosal enhancement of the urothelium, renal enlargement, and inflammatory changes in Gerota fascia and/or the renal sinus.(46) Perinephric collections can also be visualised which may require drainage to rule out an abscess.

Variant forms of Pyelonephritis include (47)

1. Hemorrhagic bacterial Nephritis
2. Focal Pyelonephritis
3. Hematogenous seeding
4. Emphysematous Pyelonephritis

Ultrasound findings are usually normal in the setting of pyelonephritis. It is useful only to exclude obstruction as a cause of Pyelonephritis. Nonspecific findings of pyelonephritis

on ultrasound include focal hypoechoic region with decreased vascular flow, renal enlargement, and loss of the sinus fat and/or cortico-medullary differentiation.(47) Ultrasound is 90% sensitive and 97% specific for pyonephrosis and a dilated collecting system can be visualised. (48) About 75% of renal abscesses occur in diabetic patients and can have insidious onset because of lack of flank pain due to diabetic neuropathy. Emphysematous Pyelonephritis or pyelitis are seen primarily in diabetic patients. CT is the imaging modality of choice. It demonstrates gas in the renal parenchyma, asymmetric renal enhancement with delayed contrast excretion and focal areas of necrosis and abscesses(49).

Extended spectrum beta lactamases

The major antibiotics used against gram negative organisms are beta lactam antibiotics. The bacteria to defend against the beta lactams produce beta lactamases. These enzymes cleave the beta lactam ring inactivating the antibiotic. The initial Beta lactamases were found in staphylococcus aureus as the beta lactams were introduced in the market. Then they were also found in organisms (Neisseria gonorrhoea and Haemophilus influenzae) that were not known to harbour the enzyme. As the newer antibiotics like Cephalosporins, carbapenems and monobactams were introduced into the market, the bacteriae adapted by producing a variety of new beta lactamases. This usually takes 2-3 years once an antibiotic is introduced. The resistance genes spread by integrons and plasmids between the same species and even cross-species. (50)

The beta lactamases are of two types

1. Metalloenzymes
2. Enzymes with serine residues at the active site

They can be classified based on the primary structure into 4 molecular classes (A-D) or based on the substrate spectrum and the way they respond to inhibitors into functional groups.

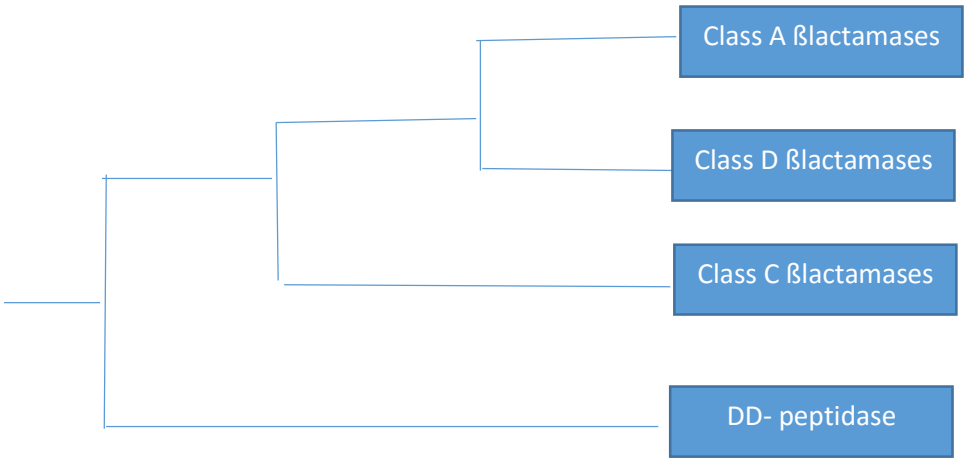
Phylogeny based on Structure of the serine beta lactamases

The Serine beta lactamases use an active serine site to cleave the beta lactam ring. Based on the sequence they have been classified into

1. Class A ß Lactamases
2. Class C ß Lactamases
3. Class D ß Lactamases

Hall and barlow constructed a phylogenetic tree of the above based on the alignment of proteins and their structure. It showed that the serine proteases are related to the DD peptidases. It also showed the order of descent not the branch length. It describes the Class C evolving earlier than Class A and D from a common ancestor. (51)

Figure 5 Phylogenetic Tree of the Serine Proteases



The Class B ß Lactamases are metalloenzymes. Though the class B andC have a broader spectrum of activity, they are usually confined to a few organisms.

Types of Extended Spectrum Beta Lactamases

TEM Type Extended Spectrum Beta lactamases (Class A)

These are created by amino acid substitutions in the TEM-1 beta lactamases. The ones with extended spectrum activity have changes in the active site of the enzyme(52). This confers action on the oxyimino Beta lactams. The opening of the active site confers susceptibility to the beta lactamase inhibitors like clavulinic acid. Extended spectrum beta lactamases are usually not compatible with inhibitor resistance. Around 220 TEM enzymes have been described of which TEM 10, TEM 12 and TEM-26 are common.

SHV Type Extended spectrum Beta lactamases (Class A)

The SHV-1 Type is similar to the TEM-1 sharing around 68% of the amino acids(53). They too have a few amino acid substitution around the active site making their activity against beta lactamases extended spectrum. 190 varieties have been described among which SHV-2, SHV-5, SHV-7 and SHF-12 are the commonest. Not all of the them are ESBL. Few of them are active only against penicillins and narrow spectrum cephalosporins.

CTX- M Type Extended Spectrum Beta Lactamases (Class A)

This group has greater activity against Cefotaxime than other Oxyimino beta lactam substrates. However few of them hydrolyse Ceftazidime more efficiently. They acquire the beta lactamase gene by plasmid mediated transfer from kluyvera species which are commensals. Around 160 enzymes are known currently.They are the most common

Extended spectrum beta lactamases worldwide. The spread of this group is not because they cleave the beta lactams better but rather efficient spread by replicons. (54)

OXA- Type Extended Spectrum Beta lactamases (Class D)

They are plasmid mediated. They can hydrolyse oxacillin and related anti-staphylococcal penicillins. They are relatively resistant to inhibition by Clavulinic acid. Few of them have amino acid substitutions which confer extended spectrum activity.

Carbapenemases

These group of enzymes are active against oxyimino beta lactams, cephamycins and carbapenems. Plasmid mediated IMP-type carbapenemases have been observed in Acinetobacter and Pseudomonas. The Klebsiella pneumonia carbapenemase is the most important enzyme in class A. It is also plasmid mediated. Though it is seen predominantly in Klebsiella, there is cross transmission to Escherichia coli, Pseudomonas, serratia and Enterobacter species.

The class B enzymes include IMP, VIM and NDM. The New Delhi metallo-beta lactamase (NDM) was first described in an Indian origin man who had travelled to New Delhi (55). In our institute we had tested 42 isolates of Escherichia coli and 134 isolates of Klebsiella pneumonia from blood culture during 2013-2015 and we screened for carbapenemase production by the carba NP test. Among them 95% (n= 167) of them had positive test. The isolates were screened specifically for the specific genes which is tabulated below.

Table 5 Distribution of carbapenemase resistant genes from organisms isolated from 2013-2015 in our institute (Adapted from sharma et al) (51)

Carbapenemase resistant genes	E. coli (n=42) n(%)	K. pneumonia (n=134) n(%)	Total N (%)
NDM	20 (48)	36 (27)	56 (32)
OXA- 48 like	8 (19)	48 (36)	56 (32)
VIM	0	2 (1)	2 (1)
NDM + VIM	7 (17)	2 (1)	5 (9)
NDM + OXA-48 like	2(5)	20 (15)	13 (13)
VIM + OXA-48 like	0 (0)	14 (10)	8(14)
NDM + VIM + OXA-48	0 (0)	14 (10)	8 (14)
All negatives *	5 (12)	6 (4)	11 6)

*All negatives- negative for IMP, NDM, VIM, OXA-48 like and KPC

These organisms are usually susceptible to aminoglycosides. Hence Amikacin can be a reasonable option. (56)

Others

Other Class A Extended spectrum Beta lactamases in Enterobacteriaceae include VEB-1 and VEB-2, GES-1, GES-2 and IBC-2. PER-1 is described in the Acinetobacter species. Other rare ones include BES-1, IBC-1 SFO-1, TLA-1

Table 6 Selected Beta lactamases (Adapted from George et al)

Molecular class	ß- lactamase	Examples	Substrates	Inhibition by clavulinic acid
A	Broad Spectrum	TEM-1, TEM-2, SHV-1	Benzylpenicillin, Aminopenicillins, Carboxypenicillins, Ureidopenicillin,, Narrow-spectrum cephalosporins	+++
	Extended spectrum	TEM family and SHV family	Substrates of broad spectrum group and oxyimino cephalosporins and monobactams	++++

		Others	Same as TEM and SHV family	++++
		CTX-M family	Substrates as the expanded group plus cefepime for few enzymes	++++
	Carbapenemase	KPC-1, KPC-2, KPC-3	Substrates of the expanded group plus Cephamycins and carbapenems	+++
B	Carbapenemase	IMP family, VIM family, GIM-1, SPM-1	Substrates of the expanded group plus Cephamycins and carbapenems	0
C	AmpC	ACC-1, ACT-1, CFE-1, CMY family, DHA-1, DHA-2, FOX family,	Substrates of expanded-spectrum group plus cephamycins	0

		LAT family, MIR-1, MOX-1, MOX-2		
D	Broad Spectrum	OXA family	Substrates of the broad-spectrum group plus cloxacillin, methicillin,and oxacillin	+
	Carbapenemase	OXA-23, OXA-24, OXA-25, OXA-26, OXA-27, OXA-40, OXA-48	Substrates of the expanded group plus Cephamycins and carbapenems	+

Treatment of Pyelonephritis

Urinary tract infections are usually caused by Enterobacteriaceae which are gram negative organisms and rarely few gram positive organisms like Enterococcus, Staphylococcus saprophyticus as described earlier. Since resistance pattern of Enterobacteriaceae varies depending on the region, local antimicrobial susceptibility patterns are important in treatment.

Table 7 Pattern of resistance among uropathogens in India

Place	**Population**	**ESBL (%)**	**Quinolones Resistance (%)**	**Reference**
Vadodara	Adults and children	58.7	-	**Raval *et al*(57)**
Aligarh	Adults and children	85	69	**Akram et al(58)**
Chandigarh	Outpatients	21.4	70	**Datta et al (59)**
Chennai	Outpatients/ Inpatients	70	-	**Bashini et al (60)**
Dehradun	Outpatients	32.08	53.91	**Biswas et al (61)**

Delhi	Outpatient females	26.9	64.2	**Kothari et al (62)**
Lucknow	Outpatient females	95.66 (4/46)	60.87	**Shaifali et al (63)**
Delhi	Children	45.1%	76	**Kaur et al (64)**
Puducherry	Inpatients	-	74.2	**Niranjan et al (65)**
Tirunelveli	Adults and Children	73.31	77.43	**Nalini et al (66)**

Since our institution is a tertiary care referral centre we have noted 21% of the blood stream isolates of Escherichia coli (n=725) and 41% of Klebsiella pneumonia (N= 349) to be susceptible to Cefpodoxime/ Ceftazidime which is a surrogate marker of extended beta lactamase production. The rates of Ciprofloxacin susceptibilty is 30% for Escherichia coli and 48% for Klebsiella pneumonia. 92% of the Escherichia coli isolated in the blood stream was susceptible to Meropenem.

Since the rates of Extended spectrum beta lactamase producing organisms are high, Carbapenems are the preferred choice of antibiotic in a complicated urinary tract infection. This also meant that the cost of treatment would be higher as the carbapenems cost more.

Cost of Pyelonephritis

Direct medical costs in Pyelonephritis would consist of cost of Antibiotics, Imaging, invasive procedures, laboratory investigations and hospital stay. Among these the most important factor is the duration of hospital stay(67). The patients with Extended spectrum beta lactamse producing organisms would require costlier drugs, with prior inappropriate therapy before presentation. Hence the duration of therapy may also increase. Diabetic patients with complications like emphysematous pyelonephritis and renal abscess would require further imaging like a computed tomography, invasive procedures like ultrasound guided aspiration or a percutaneous nephrostomy. Patients with advanced infections can present with renal failure requiring haemodialysis.

Table 8 Components of cost of illness

Direct Costs	Indirect Costs	Intangible costs
Professional fees Investigations • Invasive • Non-invasive Treatment • Drugs Food Accommodation Travel	Loss of wages Loss of wages of care giver	Pain Anxiety Loss of enjoyment Depression

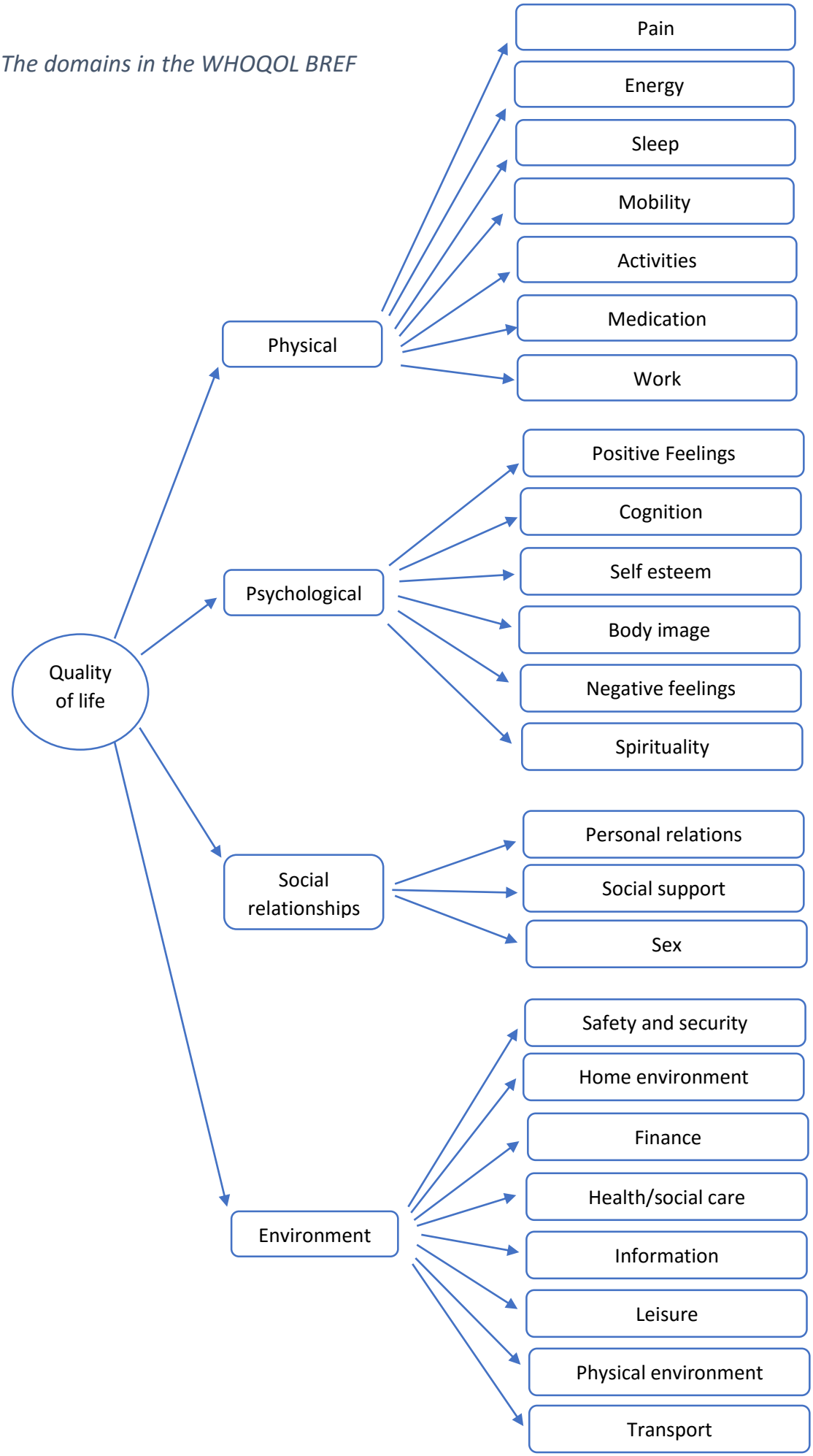
Apart from the direct medical costs, the direct non-medical costs, indirect costs and intangible costs also should be taken into consideration while evaluating the cost of hospitalisation. Direct non-medical costs include transportation to and from the hospital, cost of food and accommodation for the patient and the relatives. The indirect costs include productivity loss such as loss of wages and labour force. Intangible loss which could not be quantified include fear, anxiety and depression which may affect the long term control of Diabetes.

QUALITY OF LIFE

Health as defined by the WHO is a state of complete physical, mental and social wellbeing not just the absence of disease. (68) However health policies are not targeted towards the psychological and social aspects because it is often not measured. Often the physician overlooks these aspects as the physical body is being treated. Hence beyond the usual indicators of health like morbidity and mortality, the impact of the disease in the emotional, social life and the surrounding environment should also be considered. There are many tools which have been developed to measure these domains. One such tool was developed by the World Health Organization.(69) An abbreviated version was later released which has 26 subsets and 4 domains. Each domain has a 'raw score' which is later converted into a 'transformed score' on a scale of 0-100 to enable comparison between domains.

Transformed scale= [(Actual possible score-lowest possible score) /Possible raw score range] x 100

Figure 1The domains in the WHOQOL BREF



The WHOQOL- BREF has been validated and has been tested in two centers in India, New Delhi (N= 1456) and Chennai (N= 420).(70) The domain scores adjusted by age and sex in the centers has been described below.

Table 1WHOQOL BREF domain scores adjusted by age and sex

	Physical domain		Psychological domain		Social Domain		Environment domain	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Total	16.2	2.9	15.0	2.8	14.3	3.2	13.5	2.6
Chennai	14.8	2.3	15.4	2.2	14.8	2.9	14.8	2.5
Delhi	15.9	2.9	14.2	2.7	13.9	3.7	12.1	2.8

Adapted from Skevington et al (70)

Justification of the study

Our hypothesis was that the cost of Pyelonephritis in Diabetics would be significantly higher than those without diabetes. At present there is a lacunae in literature of the cost of illness study of pyelonephritis in Diabetes in India. The direct non-medical costs and indirect costs are often overlooked and it bears a huge burden in a developing country like India where there are daily wage labourers. We hence studied the cost of illness of a single occurrence of Pyelonephritis requiring hospitalisation among diabetics and non- diabetics. We have planned to look at the direct medical and non-medical costs, indirect costs and intangible loss. We also compared the costs of Pyelonephritis due to ESBL organisms versus the non- ESBL organisms. We wanted to observe the factors influencing the direct medical, non-medical and indirect costs and if by any means that could be reduced or altered to reduce the economic burden of the disease.

METHODS

Ethical Approval

This study was conducted after obtaining permission from the Institutional review board (IRB Number 9912 dated 05.02.2016 Appendix number 1) prior to commencement of the study.

STUDY DESIGN

Setting

The COPID study (Cost of Pyelonephritis in Type-2 Diabetes) is a prospective observational economic study. This was conducted among patients admitted in the general medical wards in Christian Medical College, Vellore (CMC). Our hospital is a tertiary care hospital primarily catering to middle and low income group patients from all over India; predominantly Tamilnadu, Andhra-Pradesh, Karnataka and the North-Eastern states. Participants were recruited between March 2016 and July 2017. The data was collected directly by the principle investigator.

Participants

The patients included in the study were those admitted within the general medical ward with a clinical and laboratory confirmed diagnosis of Upper Urinary tract infection (Pyelonephritis). Participants were eligible if they were above 18 years with symptoms of fever, lower urinary tract symptoms, renal angle tenderness, laboratory evidence of pyuria, and urine culture and/or blood culture growing an Uro-pathogenic organism. We excluded Patients who had previous urological procedures, nosocomial or catheter associated infections and those who refused

consent. As we were interested in costs we included participants from Southern states as costs such as indirect costs vary in large amount across India.

Procedure

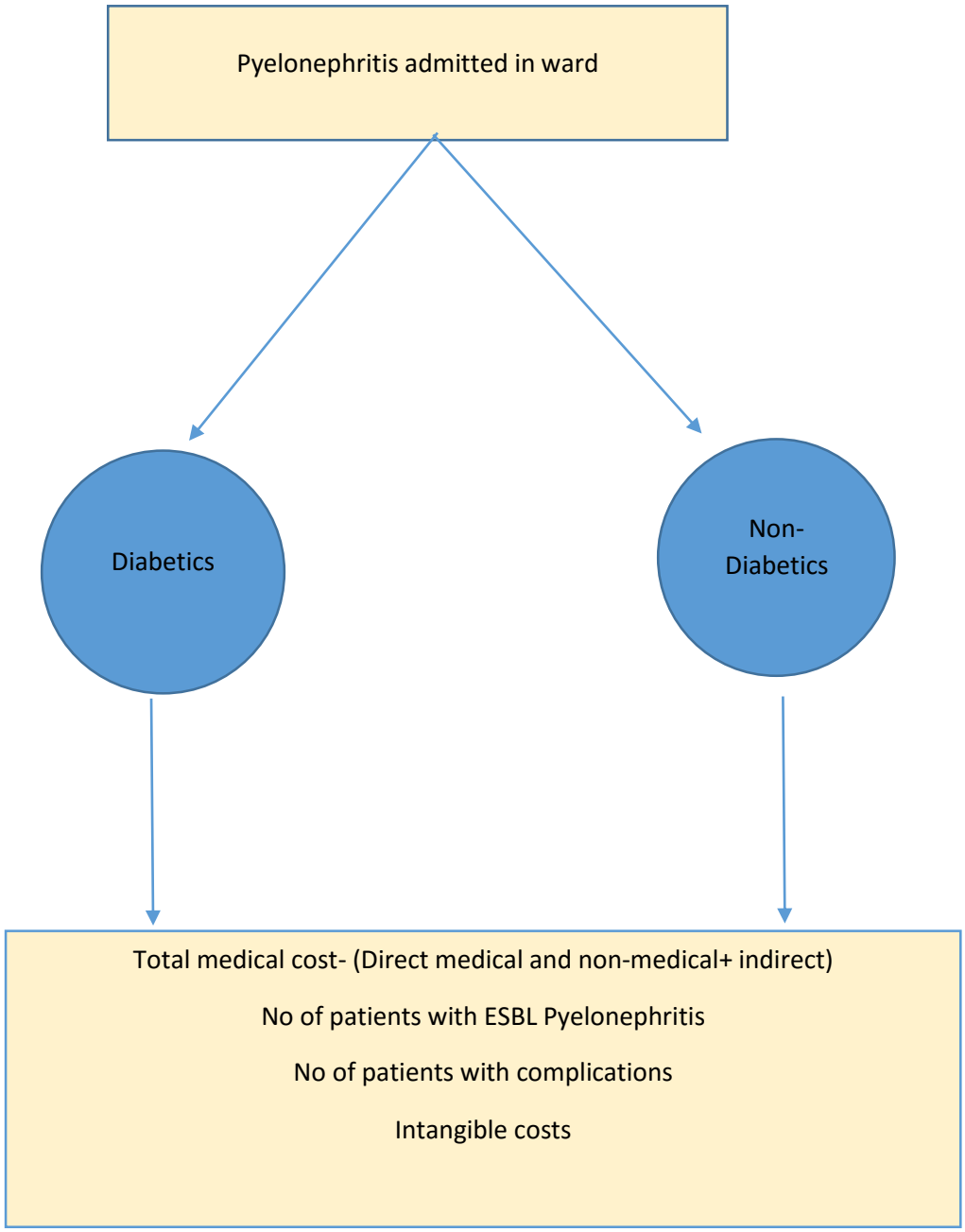
Once patients were identified, they were given the Information sheet, following which written informed consent was obtained (Copy of Information sheet in Appendix number 2). All study data were collected by the principle investigator on a specially designed Clinical Research form (CRF) (Copy of the CRF in Appendix number 3). The participants of the study were interviewed regarding risk factors for urinary tract infections, medical co-morbidities including diabetes mellitus, systemic hypertension, chronic kidney disease and heart failure. Their urinalysis including nitrites and leucocyte esterase were noted. Blood culture and urine culture data including presence of extended spectrum beta lactamase (ESBL) and Carbapenem resistant organisms (CRO) were noted. The initial empiric antibiotic chosen, antibiotics after the susceptibility of the isolate was known and after clinical stabilisation were noted. Data on complications like emphysematous pyelonephritis, renal abscess, haemodialysis and hospital acquired infections were noted and described. We also documented any surgical or radiology guided interventional procedures.

Economic Data

The economic data included their occupation, education, family income per month and participants were then stratified into the respective socio-economic class based on the modified Kuppusamy score**.** The total duration of hospital stay and the duration of antibiotics were also noted. The quality of life was assessed by the WHO

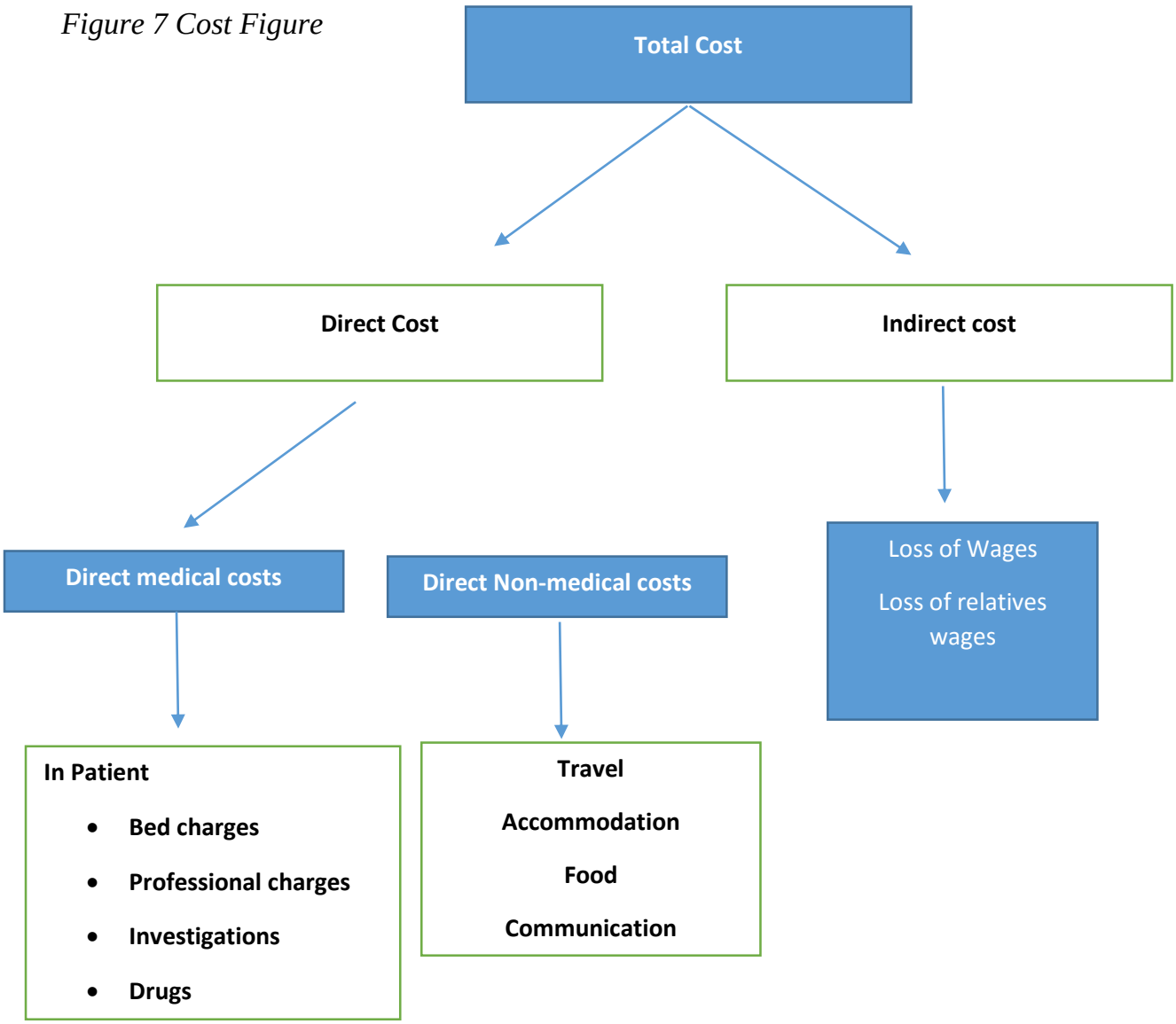
quality of life questionnaire. We used a societal perspective on costs to include both the health care costs as well as patient related costs. We used the consolidated health economic evaluation reporting standards (CHEERS) guidelines to report the data. (Appendix-9)

Figure 6 Study Outline



The participants were then interviewed regarding direct medical, non-medical and indirect costs. (*Cost figure* shown below) This was done twice, once at admission and another through a telephonic interview at the completion of therapy. The direct medical costs included bed charges, charges for laboratory investigations, invasive and non-invasive tests, drugs and professional charges. The direct non-medical costs included expenditure for travel of the patient and the relatives, food during hospital stay for the patient and relative and accommodation for the relatives. Indirect medical costs included loss of wages for the patient and the relative during the time of illness. Our time horizon was only the year of the study and as we did not have costs beyond this time period we did not discount costs.

Figure 7 Cost Figure



The primary outcome was total cost of illness for an admission for Pyelonephritis which is the direct medical, non-medical cost and the indirect costs.

The secondary outcomes included comparison of costs among participants with and without ESBL bacterial pyelonephritis as well as those with and without diabetes mellitus. We also studied the clinical outcomes such as cure, condition at discharge, and quality of life (assessed by the WHO quality of life questionnaire).(**reference)**

STATISTICAL ANALYSIS

Sample size

The primary objective is total cost of an admission for Pyelonephritis and the hypothesis was that Diabetics would have significantly higher cost compared to non-diabetics. The total cost for a single admission for Pyelonephritis was estimated to be Rs. 40,000. The Standard deviation was estimated to be 4000. The precision (d) was taken as 1000. The sample size was calculated to be 64.

Sample Size = $[(Z_\alpha)^2 \text{ X } SD^2]/ d^2 = 2^2 \text{x } 4000^2/1000^2 = 64$

Assuming loss to follow up, a sample size of 75 was taken.

Data Management

All data were collected by the principle investigator on the study CRF and then entered in Epidata 3.1 software. This was exported for analysis to SPSS version 17, IBM Corporation. All data analysis was performed by a biostatistician (1)

Data analysis

All normally distributed data were described using mean and standard deviation while non-normally distributed data by median and inter-quartile range. Qualitative data were described using counts and percentages.

Data was screened for outliers and extreme values using Box-Cox plot and histogram (for shape of the distribution). Summary statistics was used for reporting demographic and clinical characteristics. Students t-test will be used for analysis of continuous data with Normal distribution and Mann-Whitney U test for data with non- Normal distribution. Chi-square test will be performed for categorical variables and the variables which will be significant at bivariate analysis will be accessed by multivariate analysis. Cost analysis of Pyelonephritis was done between those with and without diabetes mellitus, with and without ESBL bacterial infections.

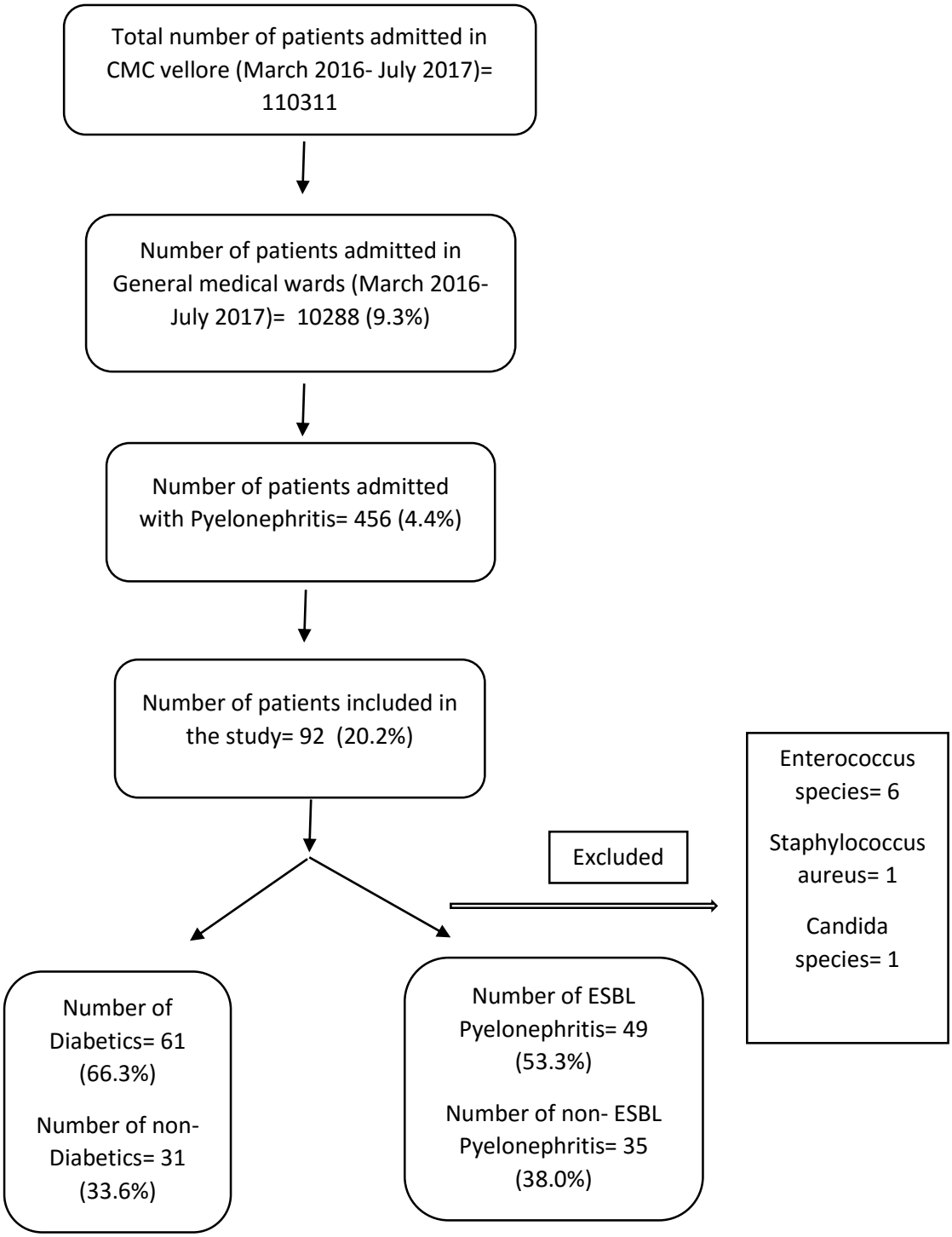
All data were reported with 95% confidence intervals. Differences were considered significant at $p<0.05$.

Funding and approval

The study was funded by an internal grant of the Hospital called the Fluid grant (22 Z 240) (appendix 4)

RESULTS

Figure 2 Strobe figure



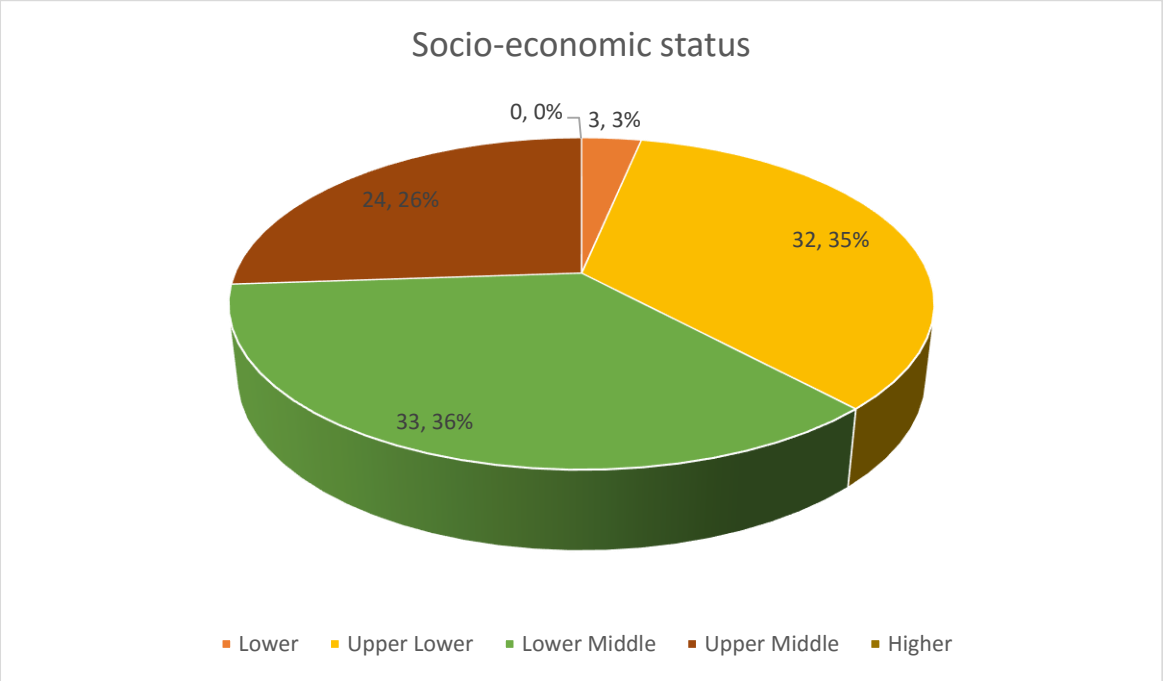
Between March 2016 and July 2017, eligible patients were screened and 92 patients were included in the study. The average age was 55.8. Around two thirds of them were diabetics. More than half of the women were postmenopausal and a fifth of them had urinary incontinence. 12% of the patients had hypotension at presentation. The mean duration of hospital stay was around 12 days and the mean number of days of intravenous antibiotics was around 14 days. There were 6 deaths among the patients in the study which amounted to 6.5% of the study population.

Table 2 Baseline Characteristics of all patients

Baseline characteristics	**N= 92**	**Percentage**
Male	39	42.4%
Female	53	57.6%
Average Age	55.8	SD- 16.53
Diabetes	61	66.3%
Average HbA1c	8.72	SD- 1.9
Hypertension	42	45.7%
Average creatinine	2.2	Median IQR- (0.82-3.08)
Ischaemic Heart disease	15	16.3%

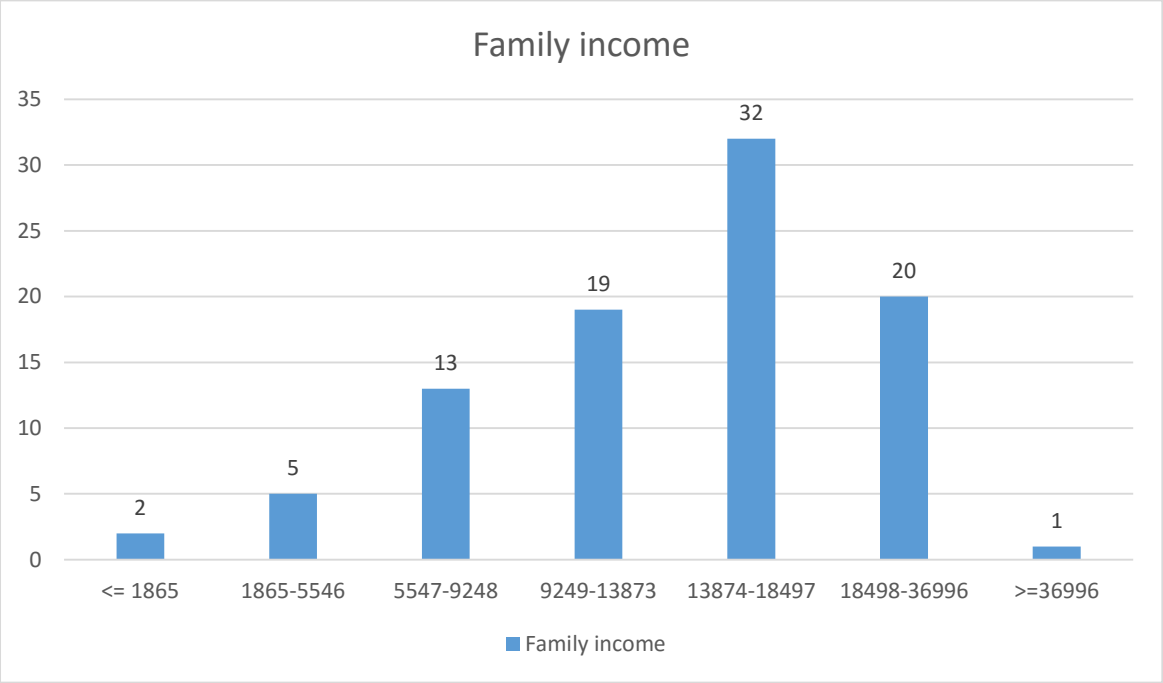
Hypotension at presentation	11	12.0%
Post-menopausal	33 (33/53)	62.3%
Urinary incontinence	10 (10/53)	18.9%
Benign prostatic hypertrophy	7 (7/39)	17.9%
Duration of hospital stay	11.89	Median IQR (7.0-15.0)
Number of days of intravenous antibiotic	13.99	Median IQR (7.0-14.0)
Number of deaths	6	6.5%

Figure 3 Distribution of Socio-economic status



One third of the study population was from lower middle socio-economic status by the kuppusamy scale while another third was from the upper lower socio-economic status.

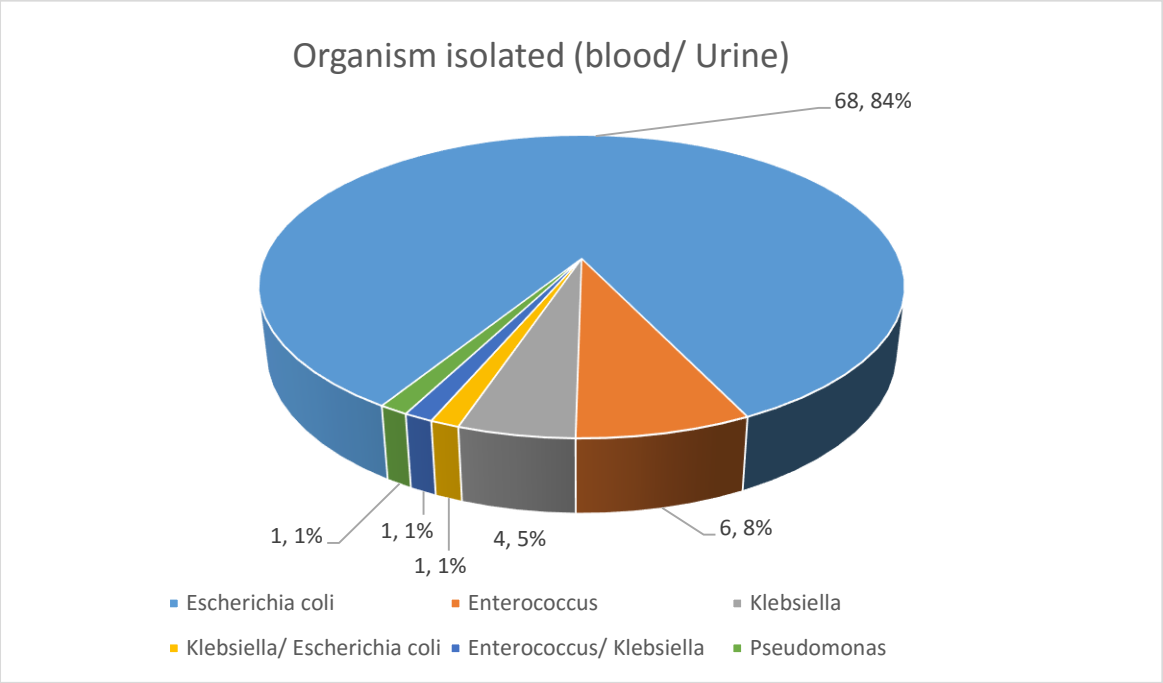
Figure 4 Distribution of Monthly Family Income



Costs in INR

The distribution of monthly family income showed that predominantly the study population was from the middle socio-economic status.

Figure 5 Distribution of Organisms isolated



Escherichia coli was the most common organism isolated followed by Enterococcus and Klebsiella. 53.3% of the gram negative isolated were producing extended spectrum beta lactamases.

Table 3 Comparison of baseline characteristics of Diabetics versus Non-Diabetics

Baseline characteristics	Diabetics	Non-Diabetics
Male	24 (26.0%)	15 (16.3%)
Female	37 (40.2%)	16 (17.3%)
Average Age	58.8 (SD-12.5)	49.9 (SD- 21.5)
Average HbA1c	9.3 (SD- 2.7)	5.9 (SD- 0.7)
Hypertension	35 (38.0%)	7 (7.6%)
Average creatinine	2.3	2.0
Ischaemic Heart disease	12 (13.0)	3 (3.2%)
Hypotension at presentation	11 (12.0%)	0 (0%)
Duration of hospital stay	12.8 (SD- 7.5)	10.2 (SD- 5.8)
Number of days of intravenous antibiotic	14.8 (SD- 8.4)	12.3 (SD- 8.4)

Comparing Diabetics and Non-diabetics in the study, the mean age of the diabetics was 10 years more than the non-diabetics. All patients who had hypotension were diabetics. The diabetics had more comorbidities like hypertension and ischaemic heart disease. Renal dysfunction was comparable in both the groups.

Table 4 Comparing baseline characteristics of ESBL versus Non- ESBL producing organisms

Baseline characteristics	ESBL	Non-ESBL
Male	26 (30.9%)	11 (13.1%)
Female	25 (29.8%)	24 (28.6%)
Average Age	57.5 (SD- 13.6)	53.5 (SD- 19.8)
Diabetes	34 (69.4%)	24 (68.5%)
Average HbA1c	8.9	8.4
Hypertension	24	14
Average creatinine	2.6	1.8
Ischaemic Heart disease	8	5
Hypotension at presentation	8	3
Duration of hospital stay	12.4	11.5
Number of days of intravenous antibiotics	15.5	11.8

Comparing Pyelonephritis caused by ESBL versus non-ESBL organisms, both groups had comparable age groups and diabetics. The ESBL group had a worse renal function at presentation. The duration of intravenous antibiotics was longer in the ESBL group.

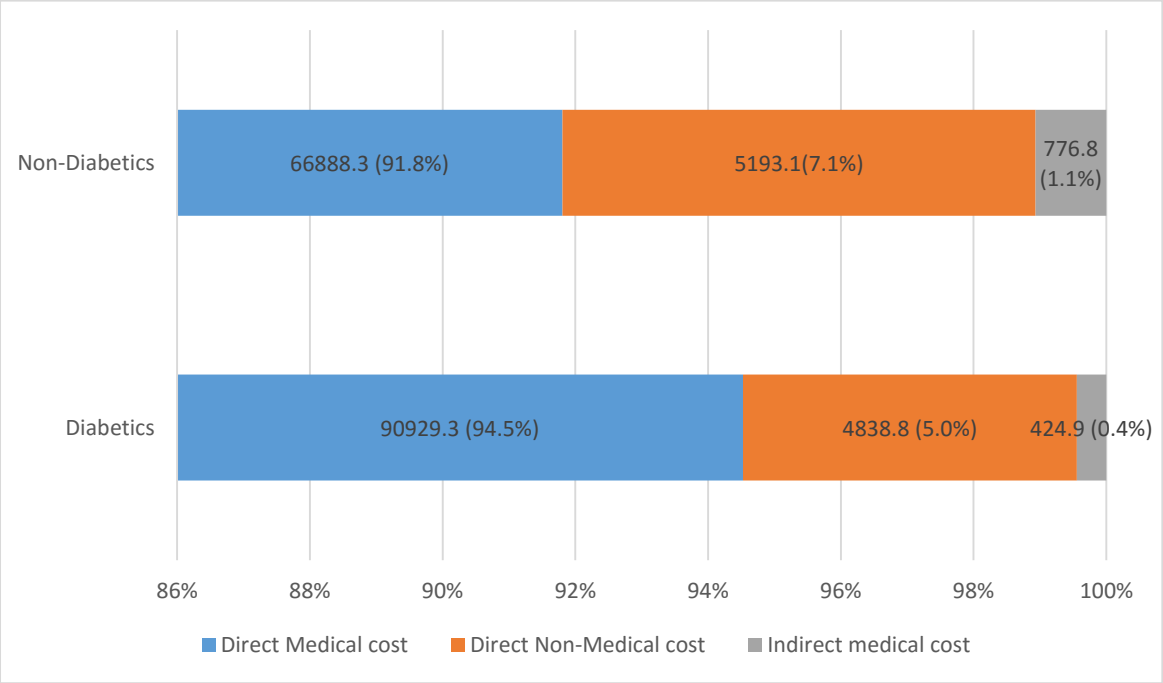
Table 5Cost Description of cost in Diabetics versus Non-Diabetics (in INR)

Direct Medical cost			
	Diabetics	**Non-Diabetics**	**P-value**
Mean	90929.3	66888.3	0.2017
Median	56332.0	47656.0	0.6437
Standard Deviation	97442.7	50570.5	-
Direct Non-medical cost			
	Diabetics	**Non-Diabetics**	**P-value**
Mean	4838.8	5193.1	0.7089
Median	3500.0	4520.0	0.2839
Standard Deviation	4167.1	4524.3	-
Indirect Medical Cost			
	Diabetics	**Non-Diabetics**	**P-value**
Mean	424.9	776.8	0.2430
Median	0.0	0.0	1.0
Standard Deviation	804.8	2074.5	-
Overall cost			
	Diabetics	**Non-Diabetics**	**P-value**
Mean	96193.0	72858.2	0.2284
Median	60632.0	52547.0	0.6754
Standard Deviation	99722.2	54720.2	-

Costs in INR

The mean cost of a diabetic with pyelonephritis was Rs.96193.0 and for a non-Diabetic it was Rs.72858.2. The direct medical cost accounted to Rs.90929.3 for the diabetics and Rs.66888.3for a non-Diabetic.

Figure 6 Comparing Costs between Diabetics and Non-Diabetics



Costs in INR

Direct medical costs accounted to more than 90% of the overall costs in both diabetic and non-diabetics. Direct non-medical costs accounted to around 7% in the non-diabetics group and 5% in the diabetic group. Indirect medical costs were around 1% in the non-diabetic group and less than 0.5% in the diabetic group.

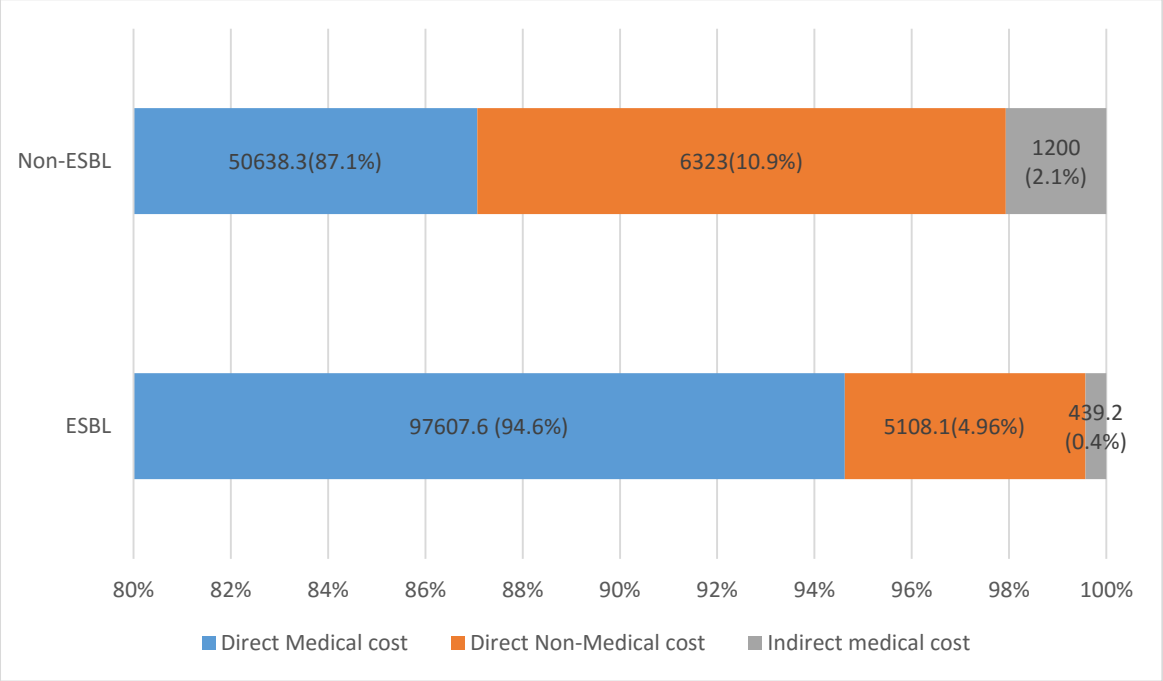
Table 6 Cost Description in ESBL producing versus Non-ESBL producing organisms

Direct Medical cost			
	ESBL	**Non-ESBL**	**P-value**
Mean	97607.6	50638.3	0.0128
Median	60945.0	30393.5	0.1018
Standard Deviation	100050.4	51509.0	-
Direct Non-medical cost			
	ESBL	**Non-ESBL**	**P-value**
Mean	5108.1	6323.0	0.3774
Median	4520.0	3395.0	0.4136
Standard Deviation	3815.3	8469.7	-
Indirect Medical Cost			
	ESBL	**Non-ESBL**	**P-value**
Mean	439.2	1200.0	0.5799
Median	0.0	0.0	1.0
Standard Deviation	850.4	2248.6	-
Overall cost			
	ESBL	**Non-ESBL**	**P-value**
Mean	103154.9	58161.3	0.0231
Median	67945.0	34303.5	0.0872
Standard Deviation	102280.9	61838.4	-

Costs in INR

The overall cost for an admission for pyelonephritis caused by an ESBL producing organism was Rs.103154.9 and in comparison, that for non-ESBL producing organism was Rs.58161.3 which was statistically significant. The direct medical cost in a patient with pyelonephritis caused by an ESBL producing organism was Rs.97607.6 compared to Rs.50638.3 for a non-ESBL producing organism which was also statistically significant.

Figure 7 Comparing costs between ESBL and Non-ESBL



Costs in INR

The direct medical cost contributed close to 95% of the overall cost in the ESBL group whereas the non ESBL group it accounted to around 90%. Direct non-medical costs accounted to 10% in the Non-ESBL group and 5%in the ESBL group. The indirect costs was around 2% in the Non-ESBL group and less than 0.5% in the ESBL group.

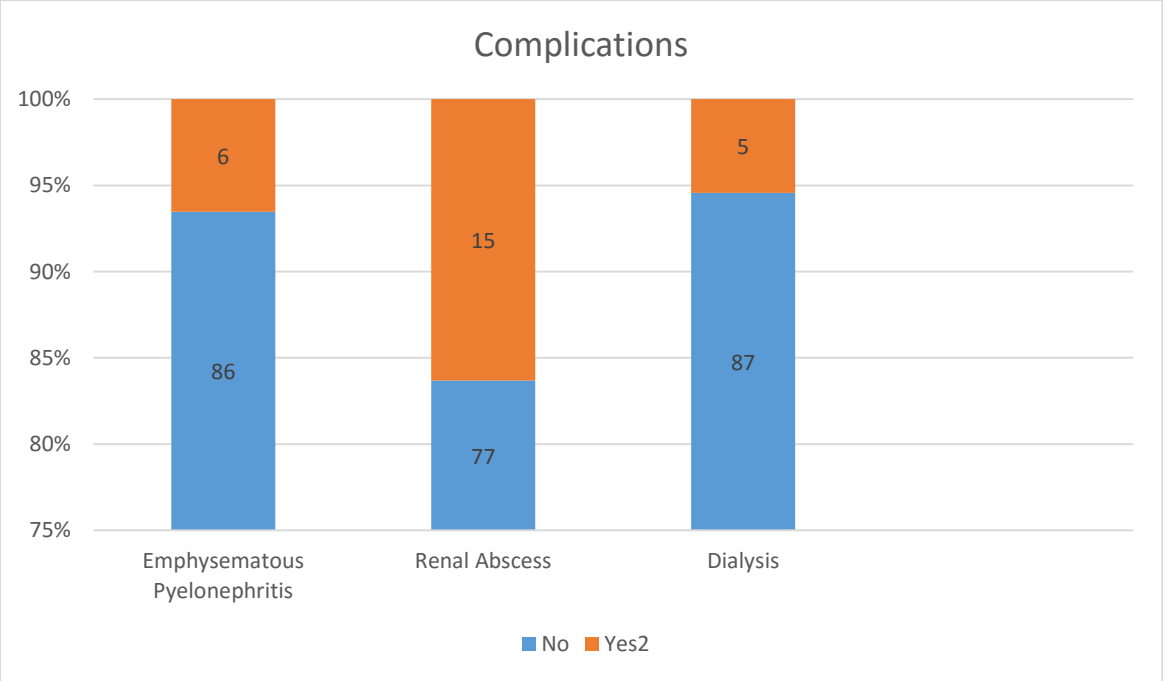
Table 7Four way cost comparison of Diabetics, Non-Diabetics, ESBL and Non-ESBL (in INR)

Direct Medical Cost					
	Diabetics/ ESBL	Diabetics/ Non-ESBL	Non-Diabetics/ ESBL	Non-Diabetics/ Non-ESBL	P-value
Mean	110726.5	70315.5	71370.0	59166.4	0.060
Median	74385.0	45255.5	50093.0	47656.0	-
Standard deviation	115641.5	64007.0	51016.0	47992.6	-
Direct Non-medical cost					
	Diabetics/ ESBL	Diabetics/ Non-ESBL	Non-Diabetics/ ESBL	Non-Diabetics/ Non-ESBL	P-value
Mean	5151..9	4571.3	5020.5	4363.3	0.679
Median	4302.5	3370.0	4545.0	3565.0	-
Standard deviation	4096.1	4507.2	3297.3	2915.7	-
Indirect Medical cost					
	Diabetics/ ESBL	Diabetics/ Non-ESBL	Non-Diabetics/ ESBL	Non-Diabetics/ Non-ESBL	P-value
Mean	489.4	320.0	338.8	1156.4	0.837
Median	0.0	0.0	0.0	0.0	-
Standard deviation	872.2	710.7	821.6	2983.2	-
Overall cost					
	Diabetics/ ESBL	Diabetics/ Non-ESBL	Non-Diabetics/ ESBL	Non-Diabetics/ Non-ESBL	P-value
	116367.7	75206.8	76729.3	64686.0	0.057
Mean	78814.5	48213.0	52653.0	51556.0	-
Median	118138.0	66132.7	52853.1	52875.8	-
Standard deviation	116367.7	75206.8	76729.3	64686.0	-

Costs in INR

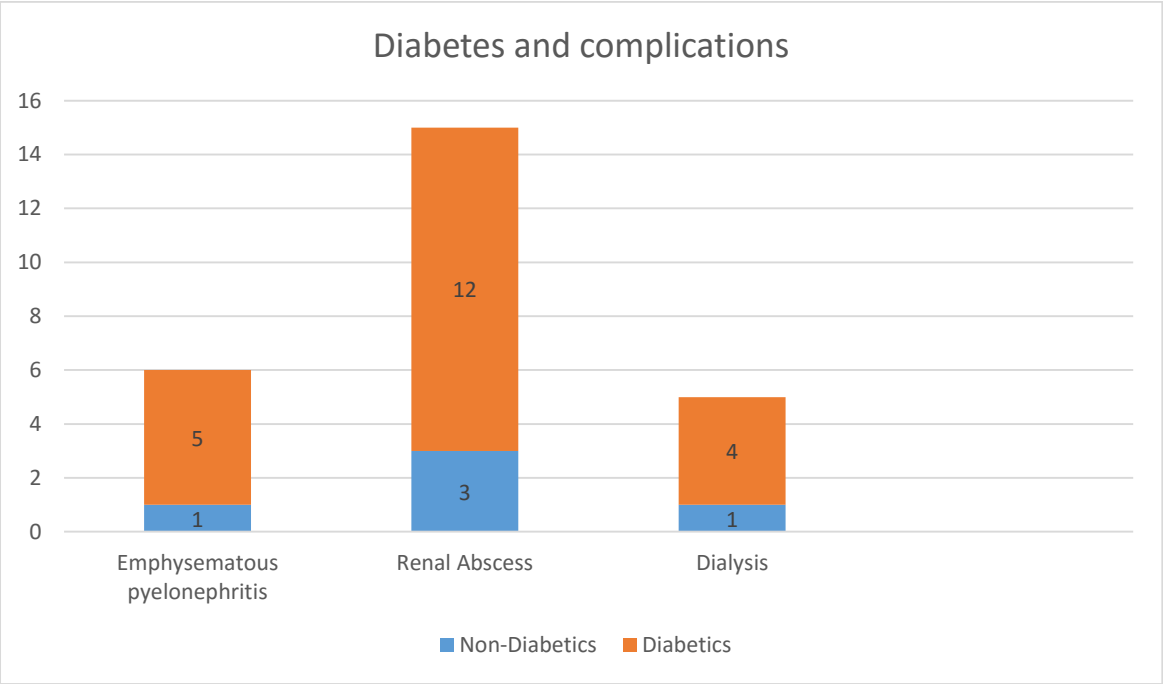
The four way cost comparison between Diabetics/ESBL, Diabetics/ non-ESBL, non-Diabetics/ESBL and non-Diabetics/ non-ESBL showed that Diabetics/ ESBL had the highest mean cost with Rs.116367.7 and Non-Diabetics/ ESBL had the lowest mean cost with Rs.64686.0. However the difference by ANOVA was not statistically significant.

Figure 8 Complications of Pyelonephritis



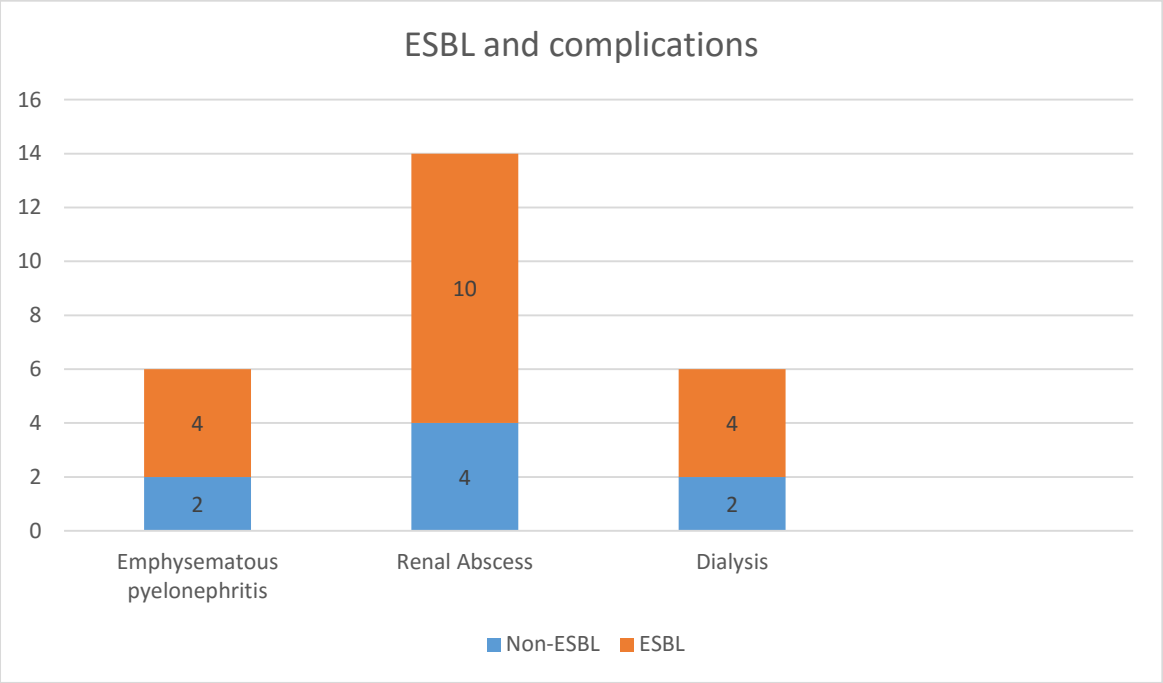
6 (6.5%) patients had emphysematous pyelonephritis while 15 (16.3%) developed renal abscess. 5 (5.4%) required renal replacement therapy.

Figure 9 Distribution of complications in Diabetics and Non-Diabetics



The complications were predominantly among the diabetics with 5 (83.3%) of the patients with emphysematous pyelonephritis 12 (80%) of the patients who developed renal abscess and 4 (80%) requiring renal replacement therapy being diabetics.

Figure 10 Distribution of complications in ESBL and Non-ESBL



The complications were more common among the ESBL group as well. 4 (66%) of the patients with emphysematous pyelonephritis, 10 (71.4%) of patients who developed renal abscesses and 4 (66.6%) of patients who required renal replacement therapy had an ESBL producing organism isolated.

Table 8 Baseline Quality of life based on WHO-QOL BREf questionnaire

	Physical health	Psychological health	Social relationships	Environment
Domain	19.7	15.5	8.9	21.5
Transformed scale	45.2	36.6	49.5	42.2

The overall quality of life was less than 50 on the transformed scale on all domains.

The psychological health was the most affected.

Figure 11 Overall Quality of life

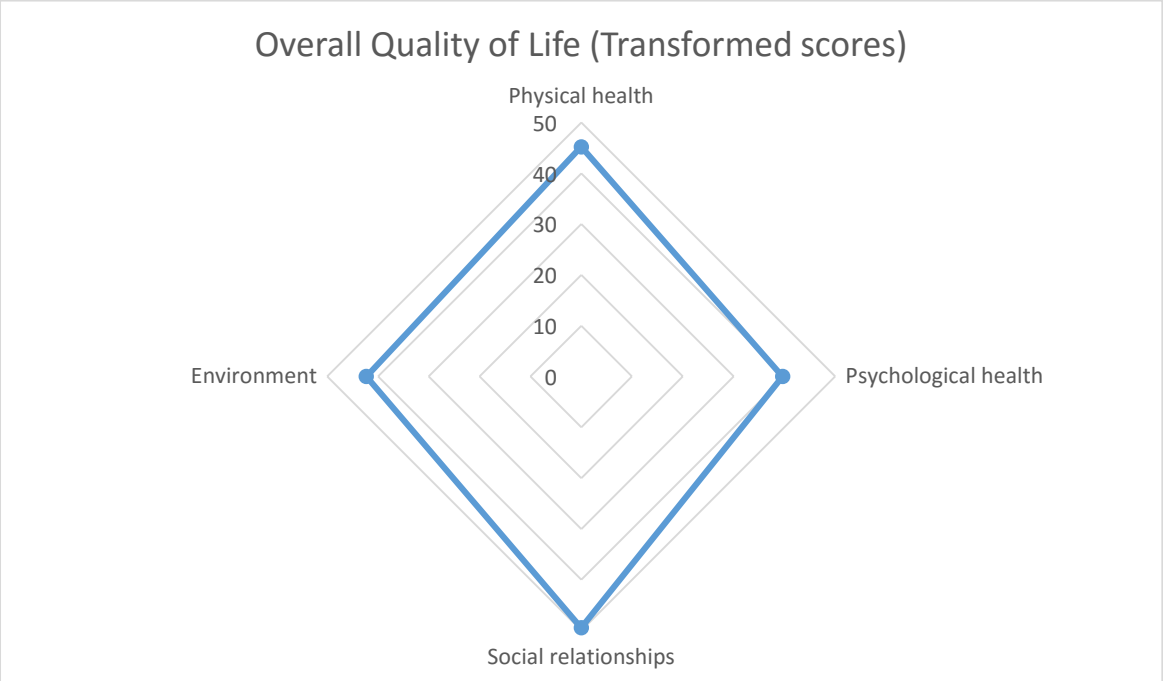


Table 9 Quality of life between Diabetics and Non-Diabetics

	Diabetics	Non-Diabetics
Physical health	43.7	48.3
Psychological health	37.9	42.8
Social relationships	47.9	52.4
Environment	40.1	46.6

Comparing the diabetics and the non-diabetics, the diabetics had a poorer quality of life and the psychological domain was the most affected.

Figure 12Qualtiy of Life in Diabetics versus Non-Diabetics

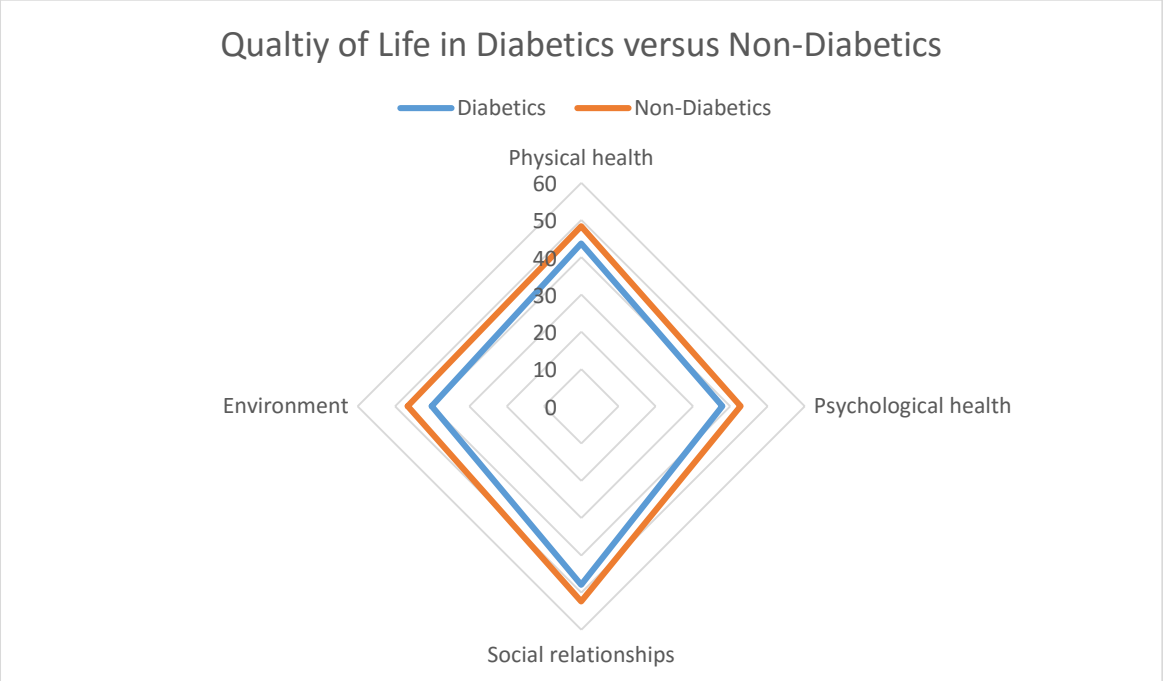
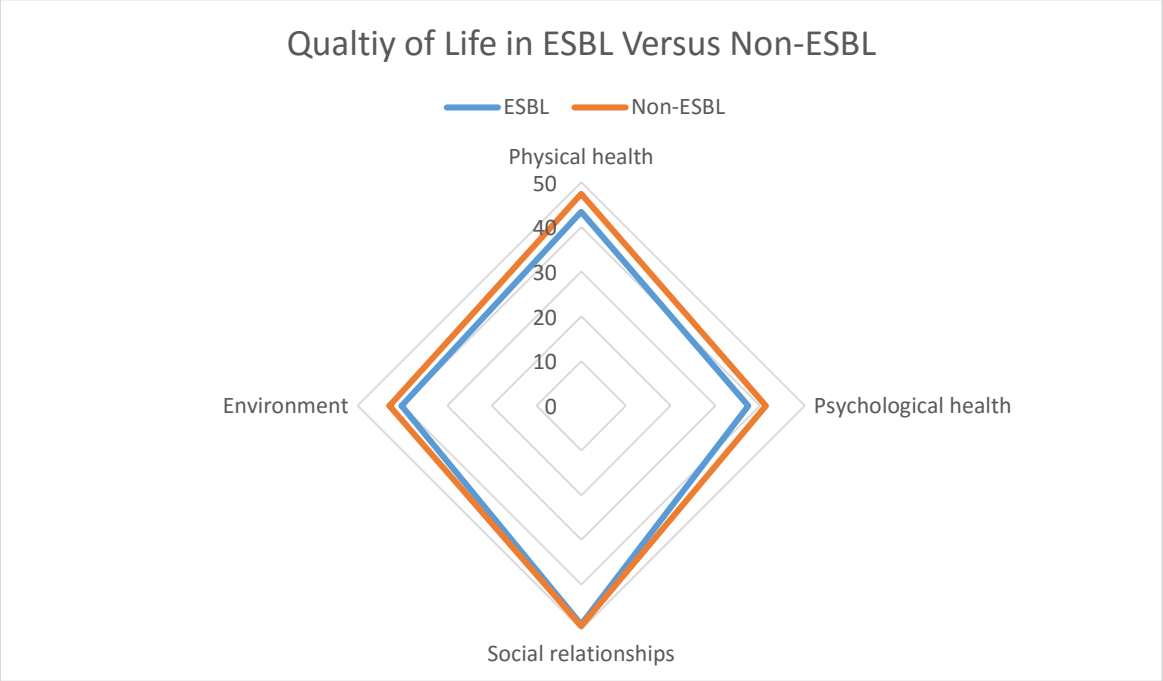


Table 10 Quality of life between ESBL and Non-ESBL

	ESBL	Non-ESBL
Physical health	43.4	47.4
Psychological health	37.4	41.3
Social relationships	48.9	49.3
Environment	40.2	42.9

Comparing the quality of life between the ESBL group and the non-ESBL group the ESBL group had a poorer quality of life. The psychological health domain was the most affected.

Figure 13 Quality of Life in ESBL Versus Non-ESBL



DISCUSSION

Medical illness in India are known to significantly affect the socio-economic health of both the patient and his or her family (71). Catastrophic health expenses are defined as 40% of family income or 10% of household expenditure. (72) On an average 4.8 % of total household consumption expenditure is spent on Out-of-pocket (OOP) health care payments.(73) The proportion of households that reported catastrophic health expenditure in the NSS survey 2009-2010 was 3.5% (3.3-3.7%). (74)

The cost of care of diabetes in India has been previously described (75). This looked at the overall costs associated with diabetes including diagnosis, medications, and treatment of complications.

The common reason for in-patient admission for diabetics in India is a urinary tract infection. Hence our study evaluated the costs associated with this problem. Urinary tract infections associated with ESBL organisms are known to be more severe and require expensive antibiotics. Hence we also studied the effect of extended spectrum beta lactamase producing organisms in this setting.

We have described the cost of a single admission for pyelonephritis in a south Indian tertiary care center. The results show that the cost for treating pyelonephritis caused by extended spectrum beta lactamase producing organism is significantly higher than a non-extended spectrum beta lactamase producing organism. The total cost is roughly around 2-3 times that of a monthly income of a middle class family. India's per capita income was Rs.1,10,023.20 (US$ 1680 in 2016). (76) The monthly per capita

expenditure in India is Rs.2630 in urban area and Rs.1430 in rural India. (77) Hence an admission for Pyelonephritis is a catastrophic health expenditure in India.

The predominant contributor to the overall cost was the direct medical cost which included bed charges, lab investigations, invasive and non-invasive tests, drugs and professional charges.

Comparison of costs from other studies

Comparing our data with the data from a survey in the United States in 2005, the annual societal cost for treatment of pyelonephritis was $US 2.14 billion ($US 3.04 billion in 2017, Rs.199.09 billion) and inpatient cost for a single patient was $US 8315.02 ($US 11819.98 Costs in 2017 are 42.2% higher than in 2000, Rs.7,74,090.49). (78) Though our costs were around 6 times lower than the cost in the United States the economic burden on a middle class family is huge. This is partly because the burden is borne by the family from savings or debt. Earlier in 1990, the annual societal cost in the United States was US$ 1.6 billion. (79) (3 billion US$ in 2017, Prices in 2017 are 87.3% higher than in 1990, Rs.196.47 billion).

Data from the Medicare diagnosis related reimbursement group in the United States in 1999 reported estimated inpatient costs of $US 2381.28 ($US 3498.82 in 2017, Prices in 2017 are 46.9% more than in 1999, Rs.2,29,137.72) without comorbidities and $US 3352.65 ($US 4926.06 in 2017, Rs.3,22,607.67) with comorbidities. (80)

Data from 1995 in the United States reported annual cost of $US 1594 million ($US 2560.29 in 2017, Prices in 2017 are 60.6% higher than in 1995, Rs.1,67,673.39) (81)

An Australian study described cost of pyelonephritis in children in which 12 children were admitted and the cost per day was $US 624.14 (Rs.40874.93) per day. However the mean duration of hospital stay was only 3 days and only 3 children received intravenous antibiotic therapy for more than 7 days. (82)

Cost of Pyelonephritis caused by Extended spectrum beta lactamase producing organism

Community acquired extended spectrum beta lactamase producing organisms is on the rise as depicted in our study group with more than half of our study population being extended spectrum beta lactamase producing. The number of days required for intravenous antimicrobial therapy was longer in patients with extended spectrum beta lactamase producing organisms and thus the cost also was significantly different. They were also sicker at admission and had more complications. The total duration of hospital stay was not significantly different between the two groups probably because few of the patients who became clinically stable chose the complete the rest of the antimicrobial therapy in a local hospital. The cost of treating an ESBL organism producing pyelonephritis was $US3658 (Rs.239562.42) in the United States. (83)

Cost of Pyelonephritis in Type 2-Diabetes Mellitus

Diabetics in the study group also had a higher cost though it was not statistically significant. A larger sample size may be required to prove the significance. The direct

medical costs again contribute significantly to the overall cost. All patients with hypotension were diabetics denoting that they were sicker than the non-diabetics at presentation. Diabetics as expected had more incidences of complications which lead to more invasive therapy, renal replacement therapy and longer anti-microbial therapy. This escalated the cost as compared to non- diabetics.

Direct Non-Medical costs

The direct non-medical costs which are often overlooked also contributed to the overall costs. This was mainly the travel and the food for the patient and the care-giver. The travel was mainly during the initial visit of the patient to the emergency department and after discharge. The day to day travel by the care-givers was negligible. We noted that our patients though hailing from faraway places do not hire a place to stay to cut down on the costs.

Indirect Medical costs

The indirect medical costs included the loss of pay for the patient and loss of wages for the caregiver. We also noted that the indirect medical cost was negligible. Many of our patients from the lower socio-economic group had a care giver who was not gainfully employed to decrease the loss of wages. The patients who had lost wages were below the 25^{th} centile. In the data from the United States however the indirect costs were

around 35% of the overall cost. (79) In 1995, indirect costs was $US 936 ($US 1503.4 in 2017, Prices in 2017 are 60.6% higher than in 1995, Rs.98457.67)

Quality of life

One of the strengths of the study was that we attempted to quantify the intangible losses in the quality of life. The quality of life was measured in 4 domains and we compared with the available Indian data. When we transformed the scores and compared the four domains, we noted that the psychological domain was scored lower than the social, physical health and the environment domains. We noted that the social domain which included social relations and social support was lower than the normal south Indian population. (70) We also compared the quality of life between the diabetics and non-diabetics. The psychological domain scored lower in the diabetics group. Comparing the ESBL and the non-ESBL group, again the psychological domain scored lower in the ESBL group. This would mean that the patient would take longer time to recover mentally and the productivity will ultimately be lesser.

LIMITATIONS

Our study had its limitations. The data was reported by the patients or the care-givers and there is an element of reporter bias. Since ours is a tertiary care institution, the patients admitted may not represent the patient in the community developing pyelonephritis. Usually patients with uncomplicated disease preferred to take the antimicrobial therapy in a local hospital. Hence the cost may be higher because of the referral bias. However this problem of possible under reporting of wages lost is known in most economic studies.

In order to reduce bias we followed the CHEERS checklist for economic studies and have followed all their reporting requirements (Appendix-9)

CONCLUSIONS

1. The mean overall cost of a single admission for pyelonephritis was Rs.88,330.2
2. The mean overall cost of an admission for a patient with Diabetes mellitus with Pyelonephritis was Rs.96,193.0
3. The mean overall cost of patient admitted with Pyelonephritis caused by extended spectrum beta-lactamase producing organism was Rs.1,03,154.9 which was significantly more than that caused by a non-extended spectrum beta lactamase producing organism.

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APPENDIX-1 Acceptance letter by the Institutional Review Board

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho MS Ortho DNB Ortho.
Chairperson, Research Committee & Principal

Dr. Biju George, MBBS., MD., DM
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

February 12, 2016.

DR. Ebenezer Daniel
PG Registrar,
Department of Medicine - 2,
Christian Medical College.
Vellore – 632 004.

Sub: **Fluid Research Funding: New Proposal**
Cost of acute pyelonephritis in type- 2 diabetes mellitus- a cost of illness study
DR. Ebenezer Daniel (Employment Number: 29455), Medicine Unit- 2,
Dr.Thambu David Sudarsanam (Employment Number: 30008), , Head of Medicine Unit-2 , Dr. Alice Joan Mathuram, Medicine Unit-1, Dr. Sowmya Satyendra, Medicine Unit-III, Dr. Samuel George Hansdak, Medicine Unit-IV, Dr. Ramya I, Medicine Unit-III, Dr. Selvin Sundar Raj M., Medicine Unit-2,

Ref: IRB Min. No. 9912 dated 05.02.2016

Dear DR. Ebenezer Daniel,

The Institutional Review Board **(Blue**, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "Cost of acute pyelonephritis in type- 2 diabetes mellitus- a cost of illness study" on February 05th 2016. I am quoting below the minutes of the meeting.

The Committee raises the following queries:

1. Are you taking only general wards
2. When you take indirect costs what all are you looking at
3. How will you distinguish pyelonephritis from UTI
4. Do all the units have a standard policy for treatment
5. When will be the QOL questionnaire given and what is the point of administering this questionnaire
6. Title – cost of acute pyelonephritis does not seem right.
7. Written everything in past tense
8. Are you going to include your own patients in this study
9. When will the consent be taken
10. Family income needs to be changed

1 of 2

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho MS Ortho DNB Ortho.
Chairperson, Research Committee & Principal

Dr. Biju George, MBBS., MD., DM
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

11. 2000 put as upper class – not correct now
12. Tamil version – few mistakes present

Drs. Ebenezer Daniel, and Selvin Sundar Raj M were present during the presentation of the proposal and satisfactorily responded to the queries raised by the Members. After discussion, it was resolved to **ACCEPT the proposal after receiving the suggested modifications and answers to the queries.**

Note:
1. Kindly HIGHLIGHT the modifications in the revised proposal.
2. Keep a covering letter and point out the answer to the queries.
3. Reply to the queries should be submitted within 3 months duration from the time of the thesis/ protocol presentation, if not the thesis/protocol have to be resubmitted to the IRB.
4. The checklist has to be sent along with the answers to queries.

Email the details to research@cmcvellore.ac.in and send a hard copy through internal dispatch to Dr. Biju George, Addl. Vice-Principal (Research), Principal's Office, CMC.

Yours sincerely,

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

Dr. BIJU GEORGE MBBS, MD, DM SECRETARY - (ETHICS COMMITTEE) Institutional Review Board, Christian Medical College, Vellore - 632 002.

Cc: Dr. Thambu David, Department of Medicine - 2, CMC Vellore.

IRB Min. No. 9912 dated 05.02.2016

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

APPENDIX-2 Patient Information Sheet

COST OF ACUTE PYELONEPHRITIS IN DIABETES- A COST OF ILLNESS STUDY

Department of Medicine,
Christian Medical College, Vellore

PATIENT INFORMATION SHEET

You are invited to be a part of a study which aims to find the cost of an admission for Pyelonephritis in Christian Medical College Vellore

What is Pyelonephritis?

Pyelonephritis is infection of the kidneys. It is usually caused by bacteria. It is more common in Diabetic patients. It can cause blood stream infection and death if untreated. . It requires antibiotics through the intravenous route to clear the infection. The infection can rarely lead to collection of pus which should be drained out.

What is the background of this study?
Diabetes is a huge economic burden. The most important component of the cost in Diabetic care is hospital admission. Pyelonephritis is an important cause of hospital admission in diabetics. Diabetic patients have more complications of pyelonephritis. The bacteria causing pyelonephritis nowadays has grown resistant to the usual antibiotics leading to use of costlier antibiotics.

What is the purpose of this study?

The aim of the study is to find the cost of a single admission for pyelonephritis. This will help us understand the burden of the disease. We also want to study if the cost is different between diabetic patients and non-diabetic patients.

If you take part what will you have to do?

If you are included in the study, you will be interviewed regarding the cost of your treatment for Pyelonephritis. This will include your travel, accommodation, medicines, blood and urine tests and loss of pay. This will be followed up by an interview by telephone assessing the impact of the disease after few weeks.

Can you withdraw from this study after it starts?

Your participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. Your refusal or withdrawal will not affect the standard of care you would receive at our institution's health services.

What will happen if you develop any study related injury?

We do not expect any untoward event to occur due to the study as there is no intervention required.

Will your personal details be kept confidential?

The results of this study will be published in a medical journal but you will not be identified by name in any publication or presentation of results.

If you have any further questions, please contact
- Dr. Ebenezer Daniel,
Department Of General Medicine,
Christian Medical College,
Vellore 632004
Telephone: 09486906628
email: ebyatvellore@gmail.com

APPENDIX-3 Performa for data collection

1. Name:
2. Age:
3. Sex:
4. Hospital Number:
5. Place:
6. Occupation:
    a. Profession (10)
    b. Semi-Profession (6)
    c. Clerical, shop owner, farmer (5)
    d. Skilled worker (4)
    e. Semi-skilled worker (3)
    f. Un-skilled worker (2)
    g. Unemployed (1)
7. Education
    a. Professional (7)
    b. Graduate (6)
    c. Intermediate/post high school diploma (5)
    d. High school (4)
    e. Middle school (3)
    f. Primary School (2)
    g. Illiterate (1)
8. Family income per month, Total=
    a. ≥36, 997 (12)
    b. 18,498-36,996 (10)
    c. 13,874-18,497 (6)
    d. 9,249-13,873 (4)
    e. 5547-9248 (3)
    f. 1866-5546 (2)
    g. ≤1865 (1)
9. Socio-Economic class (Modified Kuppusamy score)
    a. Upper (26-29)
    b. Upper Middle (16-25)
    c. Lower Middle (11-15)
    d. Upper Lower (5-10)
    e. Lower (<5)
10. Duration of Hospital stay-
11. Diabetes mellitus Type 2- yes/ no
12. Hba1c-
13. Hypertensive- yes / no
14. Creatinine-
15. Ischaemic Heart disease- yes / no
16. Previous urological procedures- yes/no
17. Risk factors for UTI 1. Present 2.Absent
    If present,

Uretheral stricture 1.Yes 2. No

Stones 1.Yes 2. No

Urinary catheter 1.Yes 2. No

Vesicoureteral reflux 1.Yes 2. No

Prostatic hypertrophy 1.Yes 2. No

Neurogenic bladder 1.Yes 2. No

18. Clinical symptoms
    a. Fever- Yes/no
    b. Flank pain- Yes/no
    c. Hypotension-Yes/no
19. For women,

Use of spermicide 1.Yes 2. No

Recent sexual intercourse 1.Yes 2. No

New sexual partner 1.Yes 2. No

UTI in the past 1 year 1.Yes 2. No

Pregnancy 1.Yes 2. No

Post menopausal 1.Yes 2. No

Urinary incontinence 1.Yes 2. No

Cystocele 1.Yes 2. No

1st UTI < 15 years of age 1.Yes 2. No

Maternal history of UTI 1.Yes 2. No

20. Urine Routine-
    WBC -
    RBC -
    Nitrite: 1. Positive 2. Negative
    Leucocyte esterase 1. Positive 2. Negative

21. Blood Culture-
    a. Organism-

b. No. Of colonies
c. ESBL- Yes/no
d. CRO- Yes/ No

22. Urine culture-
    a. No. of colonies-
    b. Organism-
    c. ESBL- Yes/no
    d. CRO- Yes/ no

23. Antibiotic used
    a. Empirical
    b. After culture reports
    c. After clinical stabilisation-
24. No. of days of Intravenous antibiotics
25. Complications
    a. Emphysematous Pyelnoephritis- Yes/no
    b. Renal abscess-- Yes/no
    c. Dialysis- Yes/no
    d. Hospital acquired infections- yes/no
26. Intervention- - Yes/no
    a. Radiological- Yes/no
    b. surgical- Yes/no

27. Direct Medical Costs
    a. In-patient:
        i. Bed charges:
        ii. Investigations
            1. Lab investigations:
            2. Non-invasive tests:
            3. Invasive tests:
        iii. Drugs:
        iv. Professional charges:
28. Direct Non-medical costs
    a. Travel:
        i. Per travel
        ii. No. of relatives
        iii. Total
    b. Food:
        i. Per day
        ii. No. of relatives
        iii. Total
    c. Accomodation:
        i. Per day
        ii. No. of relatives
        iii. Total
29. Indirect Medical costs
    a. Loss of pay:
    b. Loss of Relative's wages:
30. How was the money arranged?
    a. Savings
    b. Debt

APPENDIX- 4- Approval for Fund by the Institutional Review Board

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho MS Ortho DNB Ortho.
Chairperson, Research Committee & Principal

Dr. Biju George, MBBS., MD., DM
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

July 19, 2016

Dr. Ebenezer Daniel ,
PG Registrar,
Department of Medicine - 2,
Christian Medical College,
Vellore 632 004.

Sub: **Fluid Research Funding: New Proposal**
Cost of acute pyelonephritis in type- 2 diabetes mellitus- a cost of illness study
DR. Ebenezer Daniel (Employment Number: 29455), Medicine Unit- 2,
Dr.Thambu David Sudarsanam (Employment Number: 30008), , Head of Medicine Unit-2 , Dr. Alice Joan Mathuram, Medicine Unit-1, Dr. Sowmya Satyendra, Medicine Unit-III, Dr. Samuel George Hansdak, Medicine Unit-IV, Dr. Ramya I, Medicine Unit-III, Dr. Selvin Sundar Raj M., Medicine Unit-2,

Ref: IRB Min No: 9912 [OBSERVE] dated 05.02.2016

Dear Dr. Ebenezer Daniel,

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Biju George, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes.

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

Dr. BIJU GEORGE
MBBS., MD., DM
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Cc: Dr. Thambu David, Department of Medicine - 2, CMC

1 of 4

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

APPENDIX-5 WHO Quality of Life Questionnaire

WHOQOL-BREF

June 1997

U.S. Version

University of Washington

Seattle, Washington

United States of America

Emblem...Soul Catcher: a Northwest Coast Indian symbol of physical and mental well-being. Artist: Marvin Oliver

WHOQOL-BREF

About You

Before you begin we would like to ask you to answer a few general questions about yourself by circling the correct answer or by filling in the space provided.

1. What is your gender — Male — Female

2. What is your date of birth? _____ / _____ / _____ (Day / Month / Year)

3. What is the highest education you received?
   - None at all
   - Elementary School
   - High School
   - College

4. What is your marital status?
   - Single
   - Married
   - Living as Married
   - Separated
   - Divorced
   - Widowed

5. Are you currently ill? — Yes — No

6. If something is wrong with your health, what do you think it is? _____ illness/problem

Please read each question, assess your feelings, and circle the number on the scale that gives the best answer for you for each question.

For office use			(Please circle the number)				
			Very poor	Poor	Neither poor nor good	Good	Very Good
G1 / G1.1	1.	How would you rate your quality of life?	1	2	3	4	5

For office use			(Please circle the number)				
			Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
G4 / G2.3	2.	How satisfied are you with your health?	1	2	3	4	5

The following questions ask about **how much** you have experienced certain things in the last two weeks.

For office use			(Please circle the number)				
			Not at all	A little	A moderate amount	Very much	An extreme amount
F1.4 / F1.2.5	3.	To what extent do you feel that physical pain prevents you from doing what you need to do?	1	2	3	4	5
F11.3 / F13.1.4	4.	How much do you need any medical treatment to function in your daily life?	1	2	3	4	5
F4.1 / F6.1.2	5.	How much do you enjoy life?	1	2	3	4	5

For office use			(Please circle the number)				
			Not at all	A little	A moderate amount	Very much	An extreme amount
F24.2 / F29.1.3	6.	To what extent do you feel your life to be meaningful?	1	2	3	4	5

For office use			(Please circle the number)				
			Not at all	Slightly	A Moderate amount	Very much	Extremely
F5.2 / F7.1.6	7.	How well are you able to concentrate?	1	2	3	4	5
F16.1 / F20.1.2	8.	How safe do you feel in your daily life?	1	2	3	4	5
F22.1 / F27.1.2	9.	How healthy is your physical environment?	1	2	3	4	5

The following questions ask about **how completely** you experience or were able to do certain things in the last two weeks.

For office use			(Please circle the number)				
			Not at all	A little	Moderately	Mostly	Completely
F2.1 / F2.1.1	10.	Do you have enough energy for everyday life?	1	2	3	4	5
F7.1 / F9.1.2	11.	Are you able to accept your bodily appearance?	1	2	3	4	5
F18.1 / F23.1.1	12.	Have you enough money to meet your needs?	1	2	3	4	5

For office use			(Please circle the number)				
			Not at all	A little	Moderately	Mostly	Completely
F20.1 / F25.1.1	13.	How available to you is the information that you need in your day-to-day life?	1	2	3	4	5
F21.1 / F26.1.2	14.	To what extent do you have the opportunity for leisure activities?	1	2	3	4	5

For office use			(Please circle the number)				
			Very poor	Poor	Neither poor nor well	Well	Very well
F9.1 / F11.1.1	15.	How well are you able to get around?	1	2	3	4	5

The following questions ask you to say how **good** or **satisfied** you have felt about various aspects of your life over the last two weeks.

For office use			(Please circle the number)				
			Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
F3.3 / F4.2.2	16.	How satisfied are you with your sleep?	1	2	3	4	5
F10.3 / F12.2.3	17.	How satisfied are you with your ability to perform your daily living activities?	1	2	3	4	5
F12.4 / F16.2.1	18.	How satisfied are you with your capacity for work?	1	2	3	4	5

For office use			(Please circle the number)				
			Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
F6.4 / F8.2.2	19.	How satisfied are you with yourself?	1	2	3	4	5
F13.3 / F17.2.3	20.	How satisfied are you with your personal relationships?	1	2	3	4	5
F15.3 / F3.2.1	21.	How satisfied are you with your sex life?	1	2	3	4	5
F14.4 / F18.2.5	22.	How satisfied are you with the support you get from your friends?	1	2	3	4	5
F17.3 / F21.2.2	23.	How satisfied are you with the conditions of your living place?	1	2	3	4	5
F19.3 / F24.2.1	24.	How satisfied are you with your access to health services?	1	2	3	4	5
F.23.3 / F28.2.2	25.	How satisfied are you with your mode of transportation?	1	2	3	4	5

The follow question refers to **how often** you have felt or experienced certain things in the last two weeks.

For office use		(Please circle the number)				
		Never	Seldom	Quite often	Very often	Always
F8.1 / F10.1.2	26. How often do you have negative feelings, such as blue mood, despair, anxiety, depression?	1	2	3	4	5

Did someone help you to fill out this form? *(Please circle Yes or No)* Yes No

How long did it take to fill out this form? _____

THANK YOU FOR YOUR HELP

WHOQOL-BREF Scoring

The WHOQOL-Bref, still in field trials, is a subset of 26 items taken from the WHOQOL-100. The same steps for the scoring WHOQOL-100 should be followed to achieve scores for the Bref. Although scoring the Bref is identical to scoring the WHOQOL-100, there are some differences that need to be addressed:

- The WHOQOL-Bref does not have facet scores
- Mean substitutions are recommended for Domain 1 *Physical Health* and Domain 4 *Environment* if no more than one item is coded missing
- Only three items need to be reversed before scoring

The WHOQOL-Bref (Field Trial Version) produces a profile with four domain scores and two individually scored items about an individual's overall perception of quality of life and health. The four domain scores are scaled in a positive direction with higher scores indicating a higher quality of life. Three items of the Bref must be reversed before scoring. They can be seen in Table 9, indicated by the "- (reverse)" denotation in the *Direction of scaling* column.

TABLE 9. Scoring Domains of the WHOQOL-BREF

Domains and questions 236/BREF		Direction of scaling	Raw domain score	Raw item score
Overall Quality of Life and General Health			...(2-10)	
G1.1/B1	How would you rate your quality of life?	+		...(1-5)
G2.3/B2	How satisfied are you with your health?	+		...(1-5)
Domain 1	Physical Health		...(7-35)	
F1.2.5/B3	To what extent do you feel that physical pain prevents you from doing what you need to do?	-(reverse)		...(1-5)
F13.1.4/B4	How much do you need any medical treatment to function in your daily life?	-(reverse)		...(1-5)
F2.1.1/B10	Do you have enough energy for everyday life?	+		...(1-5)
F11.1.1/B15	How well are you able to get around?	+		...(1-5)
F4.1.1/B16	How satisfied are you with your sleep	+		...(1-5)
F12.2.3/B17	How satisfied are you with your ability to perform your daily living activities?	+		...(1-5)
F16.2.1/B18	How satisfied are you with your capacity for work?	+		...(1-5)
Domain 2	Psychological		...(6-30)	
F6.1.2/B5	How much do you enjoy life?	+		...(1-5)
F29.1.3/B6	To what extent do you feel your life to be meaningful?	+		...(1-5)
F7.1.6/B7	How well are you able to concentrate?	+		...(1-5)
F9.1.2/B11	Are you able to accept your bodily appearance?	+		...(1-5)
F8.2.1/B19	How satisfied are you with yourself?	+		...(1-5)
F10.1.2/B26	How often do you have negative feelings such as blue mood, despair, anxiety, depression?	- (reverse)		...(1-5)
Domain 3	Social relationships		...(3-15)	
F17.1.3/B20	How satisfied are you with your personal relationships?	+		...(1-5)
F3.2.1/B21	How satisfied are you with your sex life?	+		...(1-5)
F18.2.5/B22	How satisfied are with the support you get from your friends?	+		...(1-5)

Domains and questions 236/BREF		Direction of scaling	Raw domain score	Raw item score
Domain 4	Environment		....(8-40)	
F20.1.2/B8	How safe do you feel in your daily life?	+		....(1-5)
F27.1.2/B9	How healthy is your physical environment?	+		....(1-5)
F23.1.1/B12	Have you enough money to meet your needs?	+		....(1-5)
F25.1.1/B13	How available to you is the information that you need in your daily-to-day life?	+		....(1-5)
F26.1.2/B14	To what extent do you have the opportunity for leisure activities?	+		....(1-5)
F21.2.2/B23	How satisfied are you with the condition of your living place?	+		....(1-5)
F24.2.1/B24	How satisfied are you with your access to health services?	+		....(1-5)
F28.2.2/B25	How satisfied are you with your transport?	+		....(1-5)

If no more than one item from the *Physical Health* or *Environment* domains has been coded as missing, we recommend that a domain score be calculated by substituting a person-specific average across the completed items in the same scale. For example, if a respondent does not have a value for item B16 *How satisfied are you with your sleep?* in the Physical Health domain, but has answered all of the other items in that domain, then the value for item B16 would be the average of the remaining 6 items. If two or more items are coded missing in these two domains, the domain score should not be calculated, likewise if any items are coded missing in the *Psychological* and *Social Relationships* domains, a domain score for that respondent would not be calculated.

After item recoding and handling of missing data, a raw score is computed by a simple algebraic sum of each item in each of the four domains. Once complete, check the frequencies of each domain to be sure that the scores are within the correct range indicated in Table 9 *Raw domain score* column. The next step is to transform each raw scale score using the formula on page 31. The possible raw score ranges for each domain are as follows: *Physical Health*=28, *Psychological*=24, *Social Relationships*=12, and *Environment*=32.

Scoring Exercise and Test Dataset for the WHOQOL-BREF Instrument

The purpose of this scoring exercise is to help WHOQOL-Bref users to evaluate results from each step in the process of calculating the Domain summary scores of the instrument. This exercise was created for SPSS users, but with minor modifications, can be adapted for other computer programs or can be useful for those scoring the survey manually.

A test dataset and SPSS code for scoring the WHOQOL-Bref a computer diskette in this packet. The test dataset, which is called "**WQ_BREF.TXT**" on the diskette, contains data from 64 administrations of the WHOQOL-BREF. The data can be seen in *Appendix F*. The enclosed diskette also provides the user with the SPSS syntax used to:

- import raw data into SPSS format [**WQ_B_DL.SPS**]
- derive the WHOQOL-BREF domain summaries [**WQ_BREF.SPS**]

The SPSS code (called "**WQ_BREF.SPS**") on the diskette begins by labeling all items and checking for out-or-range values. It then recodes the 3 negatively stated items so that a

higher score indicates better health. The 4 domains are then scored, labeled, and transformed to a 0 to 100 scale used to interpret and compare to other validated instrument tools such as the WHOQOL-100. A copy of the SPSS syntax is reproduced in Appendix F.

Table 10 presents statistics for the transformed domains for the WHOQOL-Bref. After scoring the test dataset, the means, standard deviations, and minimum and maximum observed values should agree with those presented in Table 10

TABLE 10. Test Dataset Descriptive Statistics: WHOQOL-BREF

Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
Physical (TRANSFORMED)	64	32.14	92.86	66.7969	14.5480
Psychological (TRANSFORMED)	64	37.50	95.83	73.5026	13.7165
Social Relations (TRANSFORMED)	64	25.00	100.00	73.1771	17.0891
Environment (TRANSFORMED)	64	28.13	100.00	72.8027	14.1592
Valid N (listwise)	64				

After all necessary items have been recoded, a raw score is calculated for each facet and each domain. Both facets and domains are scored through a simple algebraic summation of each item in that scale. As stated earlier, each question contributes equally to the facet score and each facet contributes equally to the domain score. Since each facet has four items with response values of 1 through 5, the raw score for any facet must have a minimum value of 4 and a maximum value of 20 (see Table 7 on the following pages).

Transformation of Scale Scores

The next step involves transforming each raw scale score to a 0-100 scale using the formula shown below:

$$\text{Transformed Scale} = \left[\frac{(\text{Actual raw score} - \text{lowest possible raw score})}{\text{Possible raw score range}}\right] \times 100$$

where "Actual raw score" is the values achieved through summation, "lowest possible raw score" is the lowest possible value that could occur through summation (this value would be 4 for all facets), and "Possible raw score range" is the difference between the maximum possible raw score and the lowest possible raw score (this value would be 16 for all facets: 20 minus 4).

This transformation converts the lowest and highest possible scores to zero and 100, respectively. Scores between these values represent the percentage of the total possible score achieved. The WHOQOL-100 scores from other Centers may not be transformed to the 0-100 scale. The U.S. WHOQOL instruments and scoring programs have used this transformation to provide comparative data for interpretation.

Example: A Facet 1 "Pain and discomfort" raw score of 15 would be transformed as follows:

$$\text{Transformed Scale} = \left[\frac{(15 - 4)}{16}\right] \times 100 = 68.75$$

APPENDIX- 6 User Agreement for using the WHO Quality of life Questionnaire

User Agreement for "WHOQOL-100" and or WHOQOL-BREF and related materials

This agreement is between the World Health Organization ("WHO") and Dr. Ebenezer Daniel WHO hereby grants the User a nonexclusive, royalty-free license to use the World Health Organization Quality of Life Questionnaire and/or related materials (hereafter referred to as "WHOQOL-100" or "WHOQOL-BREF") in User's study outlined below. The term of this User Agreement shall be for a period of 1 year, commencing on (date) 1/3/16.

The approved study for this User Agreement is:

Study Title	Cost of Pyelonephritis in Type-2 Diabetes mellitus (COPID Study) – A cost of illness study
Principal Investigator	Dr. Ebenezer Daniel
Sample characteristics	Patients with acute pyelonephritis admitted in CMC, Vellore
Sample size	92
Treatment intervention	none (observational Study)
Total number of assessments	92
Assessment time points	At admission
"WHOQOL-100" or WHOQOL-BREF version – *Please specify language version(s) you would like to receive*	WHOQOL - BREF
Other measures	-

This User Agreement is based upon the following conditions:

1. User shall not modify, abridge, condense, translate, adapt, recast or transform the WHOQOL-100 or BREF in any manner or form, including but not limited to any minor or significant change in wording or organization, or administration procedures, of the WHOQOL-100 or BREF. If User thinks that changes are necessary for its work, or if translation is necessary, User must obtain written approval from WHO in advance of making such changes.

2. User shall not reproduce WHOQOL-100 or BREF, except for the limited purpose of generating sufficient copies for its own uses and shall in no event distribute copies of the WHOQOL-100 or BREF to third parties by sale, rental, lease, lending, or any other means. In addition, User agrees that it will not use the WHOQOL-100 or BREF for any purpose other than conducting studies as specified above, unless agreed in writing by WHO. In any event, the WHOQOL-100 or BREF should not be used for research or clinical purposes without prior written authorization from WHO.

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3. User agrees to provide WHO with an annual update regarding activities related to the WHOQOL-100 or BREF.

4. User agrees to provide WHO with a complete copy of User's raw data and data code books, including the WHOQOL-100 or BREF and any other instruments used in the study. This data set must be forwarded to WHO upon the conclusion of User's work. While User remains the owner of the data collected in User's studies, these data may be used in WHO analyses for further examining the psychometric properties of the WHOQOL-100 or BREF. WHO asserts the right to present and publish those results, with due credit to the User as the primary investigator, as part of the overall WHOQOL-100 or BREF development strategy.

5. WHO shall be responsible for preparing and publishing the overall WHOQOL-100 or BREF results under WHO copyright, including:

a. the overall strategy, administrative set-up and design of the study including the instruments employed;

b. common methods used by two or more Users;

c. the data reported from two or more Users ;

d. the comparisons made between the data reported from the Users;

e. the overall findings and conclusions.

6. User shall be responsible for publications concerning information developed exclusively by User and methods employed only by User. Publications describing results obtained by User will be published in User's name and shall include an acknowledgement of WHO. User agrees to send to WHO a copy of each such paper prior to its submission for publication.

7. WHO may terminate this User Agreement at any time, in any event. Should WHO terminate this User Agreement, User shall immediately cease all use of the WHOQOL100 or BREF and destroy or return all copies of the WHOQOL-100 or BREF. In the event of such termination, all other collateral materials shall be destroyed and no copy thereof shall be retained by User. Notwithstanding the return or destruction of the WHOQOL-100 or BREF and its collateral materials, User will continue to be bound by the terms of this User Agreement.

8. It is understood that this User Agreement does not create any employer/employee relationship. User and its affiliates are not entitled to describe themselves as staff members of WHO. User shall be solely responsible for the manner in which work on the project is carried out and accordingly shall assume full liability for any damage arising therefrom. No liability shall attach to WHO, its advisors, agents or employees.

Please confirm your agreement with the foregoing by signing and returning one copy of this letter to WHO, whereupon this letter agreement shall become a binding agreement between User and WHO.

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Date:

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By: Dr. Ebenezer Daniel
Title: Cost of Pyelonephritis in Type-2 Diabetes Mellitus (COPID Study)
Institution: CHRISTIAN MEDICAL COLLEGE, VELLORE - A cost of illness Study
Address: Department of Medicine - 2,
Christian Medical College Hospital
Vellore - 632004

Date: 1/3/16

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APPENDIX-7Abstract

COST OF PYELONEPHRITIS IN TYPE- 2 DIABETES (COPID STUDY) - A COST OF ILLNESS STUDY

Background

Expenditure for health in India is borne predominantly out-of-pocket costs. A hospital admission often drives households to poverty. Diabetes in particular has become a huge economic burden in both rural and urban India. Pyelonephritis is a frequent cause of admission in a patient with Diabetes. With the rise in the incidence of community acquired extended spectrum beta-lactamase producing organisms the cost of illness has increased.

Aim

To estimate the cost of Acute Pyelonephritis in patients with Type 2 Diabetes mellitus admitted in general medical wards

Objectives

1. To estimate the total cost of a single admission for Acute Pyelonephritis
2. To estimate the difference in cost of admission for Acute Pyelonephritis between Diabetics and Non-Diabetics
3. To find the difference of cost of admission for Acute Pyelonephritis caused by ESBL organisms and non-ESBL organisms

Methods

We conducted a prospective observational economic study of patients 18 years and above admitted with clinical features suggestive of acute pyelonephritis, laboratory evidence of pyuria and a blood culture and/or urine culture growing any uropathogenic organism. Participants were recruited from the general medical wards of the Christian medical college, Vellore, a tertiary care hospital primarily catering to middle and low income group patients from all over India, predominantly the south Indian and the north eastern states. We assessed the direct medical, direct non-medical and indirect cost for an admission for pyelonephritis. We also assessed the quality of life using the WHOQOL BREF questionnaire.

Findings

Between March 2016 and July 2017, we screened and included 92 participants for the study. The numbers of Diabetics were 61 (66.3%) and the number of pyelonephritis caused by an extended spectrum beta lactamase producing organism was 49 (53.3%). The mean overall cost of a single admission for pyelonephritis was INR 88,330.2. The mean overall cost of an admission for a patient with Diabetes mellitus with Pyelonephritis was Rs.96,193.0. The mean overall cost of patient admitted with Pyelonephritis caused by extended spectrum beta-lactamase producing organism was Rs.1,03,154.9 . The difference in cost between those without Diabetes was (Rs. 24,041, P value= 0.2017) and between those with and without ESBL infection was (Rs.46969.3, P=0.0128). The intangible costs as measured by the quality of life showed that the psychological and the social domains were particularly lower than general Indian

population. The quality of life was lower in patients with Diabetes and patients who had pyelonephritis due to an extended spectrum beta lactamase producing organism as compared to those without.

Conclusion

A single admission for a patient with pyelonephritis is a catastrophic health expenditure in the household in India. In this setting, policies should be geared towards preventing the vulnerable middle and low economic groups from being driven below the poverty line.

APPENDIX 8- Data sheet

idno	name	age	sex	hospno	place	occup	educat	income	economic	hosstay	dm	hba1c	ht	creat	ihd	pup	uti	uretheral	stones
1	savithri	60	2	111597C	Gudiyathar	10	7	6	4	8	1	12	1	0.69	1	0	2	0	0
2	Ramanamn	55	2	532349G	Kadappa	1	1	6	2	22	1	6.8	1	0.5	0	0	2	0	0
3	Malliga VS	59	2	875238D	Saravanapa	3	3	10	4	13	1	7.8	1	2.38	1	0	2	0	0
4	Kalavathi D	61	2	290858F	Vasur, Vell	3	4	3	2	13	1	7.1	1	0.9	0	0	2	0	0
5	Harikrishna	42	1	531672G	Kallikri, chi	3	4	4	3	15	1	11.8	1	5.78	0	1	1	1	0
6	Jayaraman	67	1	532148G	Kanchipura	6	5	10	4	8	1	12.2	1	3.25	1	0	2	0	0
7	Zeenath Be	56	2	453344D	Melvishara	3	3	6	3	15	1	9.7	1	4.3	0	0	2	0	0
8	Vanitha S	66	2	532101G	Pallikonda	2	2	1	2	11	1	7.4	1	1.69	0	0	2	0	0
9	Rathinam	75	2	530448G	Kaspa	6	6	6	4	20	1	14.8	0	1.24	0	0	2	0	0
10	Mohan	65	1	527871G	Chittoor	3	4	6	3	25	0	7.6	1	1.6	0	1	1	0	1
11	Daniel	65	1	761497G	Thirupathu	4	5	10	4	14	1	9.5	1	4.48	0	0	2	0	0
12	Pushparani	60	2	032838D	Odukathur	2	3	4	2	32	1		1	2.44	0	0	2	0	0
13	Baby T	19	2	532245G	Chittoor	3	6	6	3	5	0		0	0.63	0	0	2	0	0
14	Ramachanc	59	1	520027G	Gudiyathar	3	4	3	2	2	1	7.7	0	1.77	0	0	2	0	0
15	Vijaya kum	58	2	077470G	Chittoor	2	3	4	2	17	0		0	3.2	0	0	2	0	0
16	Sivalingam	58	1	531930G	Odukathur	2	3	2	2	15	1	14.5	1	3.92	0	0	2	0	0
17	Krishnan	32	1	520308G	Tiruvanama	4	5	6	3	4	0		0	1.82	0	1	1	1	0
18	Balaraman	76	1	977728F	Vellore	2	3	6	3	11	0	6	1	6.37	1	0	2	0	0
19	Ravichandr	51	1	272868B	Gudiyathar	3	4	4	3	5	1	6.3	0	0.84	0	0	2	0	0
20	Sampath	58	1	920557D	Gudiyathar	5	5	10	4	9	1	7.8	0	3.2	0	0	2	0	0
21	Rani	49	2	108605G	Vellore	3	3	4	2	6	1	12.8	0	1.82	0	0	2	0	0
22	Narayanan	71	1	534955G	Tiruvanama	3	3	4	2	7	1	5.1	0	1.05	0	0	1	0	0
23	Senthil	29	1	549611G	Tiruvanama	4	6	6	4	19	1	6.8	0	0.6	0	0	2	0	0
24	Ramya	23	2	129596B	Vellore	4	6	10	4	7	0		0	0.81	0	0	1	0	1
25	Mary	60	2	546636G	Ambur	3	4	10	4	25	1	8.4	0	2.41	0	0	1	0	0
26	Kathirvel	82	1	40000	Vellore	4	5	10	4	19	1	8	1	0.91	0	0	2	0	0
27	Kasthuri	64	2	135229G	Vellore	3	5	10	4	18	0	6.4	1	1.25	1	0	2	0	0
28	Narayanasv	77	1	269641F	Gudiyathar	3	3	4	2	13	1		1	1.24	0	0	1	0	0
29	Karpagamn	81	2	561895G	Vellore	3	3	4	2	15	0	4.7	0	0.78	0	0	2	0	0
30	Kanagaraj	81	1	539111G	Vellore	3	4	10	4	20	1	9	1	3.33	0	0	2	0	0
31	Nirmala	52	2	768263G	Vellore	3	5	10	4	5	1	12.5	1	0.59	1	0	2	0	0
32	Gandhimat	47	2	543376G	Tiruvanama	3	3	4	2	10	1	12.4	1	2.02	0	0	2	0	0
33	Mahalaksh	32	2	520911F	Vellore	3	3	3	2	4	0		0	1.13	0	0	2	0	0
34	Karpagamn	81	2	561895G	Vellore	2	2	6	2	14	0		0	0.78	0	0	2	0	0
35	Govindasw	55	1	522622F	Ponna	2	2	3	2	8	1	5.2	0	0.74	0	0	1	1	0
36	Bhuvanesh	67	2	701257A	Vellore	3	3	6	3	9	1	6.4	1	0.38	1	0	2	0	0
37	Vasundra	18	2	523413G	cuddalore	6	6	12	4	5	0	6.3	0	0.63	0	0	2	0	0
38	Deepika	18	2	523279G	Anaicut	4	5	10	4	11	0		0	1.86	0	0	2	0	0
39	Sivalingam	51	1	531930G	Anaicut	4	5	6	3	15	1	14.5	1	1.89	1	0	2	0	0
40	Mohan	54	1	210131D	Vellore	3	4	6	3	7	1	7.3	1	1.36	1	0	2	0	0
41	Ramakrishr	65	1	994180F	Chittoor	4	5	10	4	5	0	6	0	1.34	0	0	1	0	0
42	Nagaraj	72	1	070053D	Vellore	2	3	4	3	8	0	5.6	1	1.67	0	0	1	0	0
43	Chinni	44	2	704238F	chittoor	3	3	3	2	6	1	6.3	1	1.39	0	0	2	0	0
44	Jayaraman	68	1	532148G	Kanchipura	3	4	4	3	8	1	12.2	1	3.25	1	0	2	0	0
45	Parvathi	58	2	406448F	Walajapet	3	4	10	4	8	0		1	0.57	0	0	2	0	0
46	Sanjeevi Re	57	1	548471G	Chittoor	4	5	10	4	25	0		0	0.79	0	0	2	0	0
47	Elayaraja	51	1	510762G	Salem	4	5	10	4	13	0		0	3.75	0	0	2	0	0
48	Gnanaseka	60	1	774771C	Vellore	4	4	6	3	11	0		0	6.43	0	0	1	0	1
49	Vinodh	18	1	195098D	Vellore	1	2	2	1	8	0		0	0.26	0	0	2	0	0
50	Umapaty	60	1	527395G	Vellore	3	3	3	2	3	1	14.9	1	3.12	0	0	2	0	0
51	Kanchana	44	2	564736G	Katpadi	3	5	10	4	10	1	11.4	0	0.92	0	0	2	0	0
52	Indirani	74	2	354443B	Rangapura	1	1	2	1	7	1	6.3	1	1.02	0	0	1	0	0
53	Mani R	67	1	530381D	Kamavanpe	2	3	4	2	11	0	6	1	1.2	1	0	2	0	0
54	Selvi	50	2	510501G	Vellore	3	3	4	2	7	1	10.5	0	0.36	0	0	2	0	0
55	Radha	68	2	270813B	Vellore	3	3	4	2	5	1	11.8	1	0.58	1	0	2	0	0
56	Jammunab	63	2	539680G	Vellore	3	3	4	2	18	1	8	1	0.89	0	0	2	0	0
57	Jayachandr	49	1	531883G	Vellore	6	6	10	4	19	1	7.8	0	7.7	0	0	2	0	0
58	Jeevaratna	61	2	693126D	Chittoor	3	3	6	3	28	1		0		0	0	2	0	0
59	Amithamm	70	2	526261G	Kaverikupp	2	1	1	1	18	1		1	8.36	0	0	2	0	0
60	Pavithra	26	2	331326F	Vellore	4	6	6	4	7	0	5.7	0	3.13	0	0	2	0	0
61	Anandhan	52	1	108798G	Chittoor	3	4	6	3	6	0		0	7.69	0	0	2	0	0
62	Kalaiselvi	26	2	913318D	Vellore	4	6	10	4	9	0		0	0.95	0	0	1	0	0
63	Mumtaj	49	2	557355G	Vellore	3	3	6	3	6	1	6.5	0	0.72	0	0	2	0	0
64	Jayanthi	37	2	501626G	Vellore	3	3	6	3	14	1	6.7	0	0.71	0	0	2	0	0
65	Noorjahan	57	2	518193G	Chittoor	3	4	6	3	10	1	7.1	0	2.01	0	0	2	0	0
66	Saroja	64	2	402912G	Chennai	3	3	6	3	14	1	12.4	0	0.82	0	0	2	0	0
67	Joshuva	74	1	559092G	Vellore	4	4	6	3	5	0	5.9	0	0.92	0	0	2	0	0
68	Gunasunda	23	2	990483F	Arcot	3	4	6	3	13	0		0	0.31	0	0	1	0	0
69	Marry	50	2	669415G	Tiruvanama	4	3	6	3	8	1	10.8	1	1.42	1	0	2	0	0
70	Bakiyavath	53	2	559285G	Vellore	4	4	6	3	12	0	5.1	0	1.29	0	0	2	0	0
71	Bharathi	61	2	440759D	Vellore	1	3	4	2	7	0	5.7	1	1.08	0	0	2	0	0
72	Munaswarr	57	1	514167F	Chittoor	3	4	3	2	7	1	8.1	0	2.83	0	0	2	0	0
73	Anitha	27	2	549050G	Ranipet	3	3	3	2	6	1	10	0	1.04	0	0	2	0	0
74	Ellamal	80	2	541355G	Tiruvanama	3	3	3	2	3	1	7.4	0	0.5	0	0	2	0	0
75	Muthu	59	1	544004G	Tiruvanama	2	3	3	2	18	0		0	1.64	0	0	2	0	0
76	Balagangial	56	1	530423G	Kadappa	4	6	2	3	33	1	6	1	1.68	1	0	1	0	0
77	Ananthamr	66	2	523162G	Thiruvallur	3	3	4	2	4	1	12.2	0	0.67	0	0	2	0	0
78	Vishwanath	71	1	321022D	Chittoor	3	5	6	3	5	0		0	1.46	0	0	2	0	0
79	Balamma	50	2	643543G	Ranipet	2	3	3	2	7	1	7.1	1	3.08	0	0	1	0	0
80	Ambika	33	2	776432C	Gudiyathar	3	5	6	3	7	1		1	8.49	0	0	2	0	0
81	Pandian	61	1	457913D	Vellore	4	4	6	3	17	1		0	2.98	0	0	2	0	0
82	Suseela	64	2	942334F	Arcot	3	4	6	3	15	1	10.6	1	1.1	0	0	2	0	0
83	Jebamalai	85	1	853093A	Vellore	4	3	6	3	17	1	7	1	1.52	0	0	2	0	0
84	Thiruvaranj	63	1	675695B	Tiruvanama	4	4	6	3	31	1		1	5.91	0	0	2	0	1
85	Gnanaseka	65	1	774771C	Timiri, Kava	2	4	3	2	4	0		0	6.43	0	1	1	0	1
86	Aparna	21	2	237445G	Ambur	1	6	4	3	5	0		0	0.47	0	0	2	0	0
87	Annamalai	76	1	530307G	Kalambur,	3	3	10	4	14	1	10.7	0	6.6	0	0	2	0	0
88	Isha	68	2	294860	Viruthampu	1	2	10	3	8	1	9.1	1	1.49	0	0	2	0	0
89	Rukminamı	60	2	530476G	Rajakandar	1	1	4	2	20	1	8.1	0	1.72	0	0	2	0	0
90	Parvathi	49	2	526905G	Amundi	2	3	2	2	27	1	8.6	0	4.82	0	0	2	0	0
91	Rajeshwari	73	2	526495G	Arcot	3	2	6	3	5	1	11.5	1	1.77	0	0	2	0	0
92	Malliga	45	2	531606G	Thirupathu	1	3	3	2	11	1	11.8	0	2.73	1	0	2	0	0

urinary	vesireflux	prostatic	neurogenic	fever	flankpain	hypotensin	spermicide	sexual	newsexual	utipast	preg	postmeno	urinaryin	cystocele	uti1st	materuti	wbc	rbc	
0	0	0	0	1	1	0	0	0	0	1	0	1	1	0	0	0	40	1	
0	0	0	0	1	1	0	0	0	0	1	0	1	1	1	0	0	241	4	
1	0	0	0	1	1	1	0	0	0	0	0	1	0	0	0	0	58	13	
0	0	0	0	1	1	0	0	0	0	0	0	1	1	0	0	0	27	14	
1	0	1	0	1	1	0												353	41
0	0	0	0	1	1	0													
0	0	0	0	1	1	0	0	0	0	1	0	1	0	0	0	0	610	29	
1	0	0	0	1	1	0	0	0	0	0	0	1	1	0	0	0	75	143	
1	0	0	0	0	1	0	0	0	0	0	0	1	1	0	0	0	47	3	
1	0	0	0	1	0	0												16	16
0	0	0	0	1	1	1												18	14
0	0	0	0	1	1	1	0	0	0	0	0	1	0	0	0	0	2584	22	
0	0	0	0	1	1	0	0	1	1	0	1	0	0	0	0	0	16	3	
0	0	0	0	1	1	1												119	2
0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	171	5	
0	0	0	0	1	1	1												620	10
0	0	0	0	1	1	0												195	20
0	0	0	0	1	1	0													
0	0	0	0	1	1	0												676	9
0	0	1	0	1	1	0												126	7
0	0	0	0	1	1	0	0	0	0	0	0	1	0	0	0	0	9	4	
0	0	1	0	1	1	0												51	13
0	0	0	0	1	1	1												115	7
0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	7	5	
1	0	0	0	1	1	0	0	0	0	0	0	1	0	0	0	0	90	5	
0	0	0	0	1	1	0												236	4
0	0	0	0	1	1	0	0	0	0	0	0	1	0	0	0	0			
1	0	0	0	1	1	0													9
0	0	0	0	1	1	0	0	0	0	0	0	1	0	0	0	0	804	21	
0	0	0	0	1	1	0												81	46
0	0	0	0	1	1	0	0	0	0	0	0	1	0	0	0	0	263	9	
0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0			10
0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	20	7	
0	0	0	0	1	1	0	0	0	0	0	0	1	1	0	0	0	804	21	
0	0	0	0	1	1	0												397	10
0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	363	5	
0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	149	2	
0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	177	13	
0	0	0	0	1	1	0												620	10
0	0	0	0	1	1	1												454	4
0	0	1	0	1	1	0												709	15
0	0	1	0	1	1	0												14	21
0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	185	17	
0	0	0	0	1	1	0												262	5
0	0	0	0	1	1	0	0	0	0	0	0	1	0	0	0	0	1046	22	
0	0	0	0	1	1	0												82	944
0	0	0	0	1	1	0												8172	80
0	0	0	0	1	1	0												108	24
0	0	0	0	0	0	0												489	47
0	0	0	0	1	1	1												4	25
0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	72	3	
1	0	0	0	0	1	0	0	0	0	1	0	1	1	0	0	0	285	2	
0	0	0	0	1	1	0												23	4
0	0	0	0	1	1	0	0	0	0	0	0	1	0	0	0	0	61	11	
0	0	0	0	1	1	0	0	0	0	0	0	1	0	0	0	0	15	11	
0	0	0	0	1	1	1	0	0	0	0	0	1	0	0	0	0	581	5	
0	0	0	0	1	1	0												23	19
0	0	0	0	1	1	0	0	0	0	0	0	1	0	0	0	0	18	4	
0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	5231	658	
0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	173	221	
0	0	0	0	1	1	0												38	9
0	0	0	0	1	1	0	0	0	0	0	1	0	0	0	0	0	630	10	
0	0	0	0	1	1	0	0	0	0	0	0	1	0	0	0	0	91	2	
0	0	0	0	1	1	0	0	0	0	1	0	0	0	0	0	0	350	4	
0	0	0	0	1	1	0	0	0	0	0	0	1	0	0	0	0	840	4	
0	0	0	0	1	1	0	0	0	0	0	0	1	1	0	0	0	984	15	
0	0	1	0	1	1	0												163	3
0	0	0	0	1	1	0	0	0	0	0	1	0	0	0	0	0	60	2	
0	0	0	0	1	1	0	0	0	0	0	0	1	0	0	0	0	47	30	
0	0	0	0	1	1	0	0	0	0	0	0	1	0	0	0	0	378	19	
0	0	0	0	1	1	0	0	0	0	0	0	1	1	0	0	0	161	424	
0	0	0	0	1	1	1												140	12
0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	13	5	
0	0	0	0	1	1	0	0	0	0	0	0	1	0	0	0	0	149	21	
0	0	0	0	1	1	0												159	16
1	0	0	0	1	1	0												490	4
0	0	0	0	1	1	0	0	0	0	0	0	1	1	0	0	0			1
0	0	0	0	1	1	0												208	5
0	0	0	0	1	1	0	0	0	0	0	0	1	0	1	0	0	28	4	
0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	1285	10	
0	0	0	0	1	1	0												52	1
0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	214	13	
0	0	1	0	1	1	0												89	61
0	0	0	0	1	1	0													
1	0	0	0	1	1	0												24	15
0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	114	17	
0	0	0	0	1	1	0												369	486
0	0	0	0	1	1	1	0	0	0	0	0	1	0	0	0	0	2610	45	
0	0	0	0	1	1	0	0	0	0	0	0	1	0	0	0	0	49	3	
0	0	0	0	1	1	0	0	0	0	0	0	1	0	0	0	0	1568	2329	
0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	1	1	4890	6	
0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	368	5	

nitrite	leucocyte	bccolonies	bcorgan	bcesbl	bcro	uccolonies	ucorgan	ucesbl	ucro	empirical	atrculture	atrclinica	venousday	emphypyel	renal	dialysis	hosinfect	interventi	radiologic
2	1		E.coli	1	0	10	E.coli	1	0	Meropener	Meropener	Meropener	14	0	0	0	0	0	0
2	1		E.coli	1	0	10	E.coli	1	0	Meropener	Meropener	Meropener	22	0	1	0	0	1	1
2	1		E.coli	1	0	10	E.coli	1	0	Meropener	Meropener	Meropener	42	0	1	0	0	0	0
2	1		E.coli	1	0	10	E.coli	1	0	Ertapenem	Meropener	Meropener	14	0	0	0	0	0	0
2	1		E.coli	0	0	10	E.coli	0	0	Meropener	Piperacillin	Piperacillin	10	0	0	0	0	0	0
			No growth			1	E.coli	1	0	Meropener	Meropener	Meropener	16	0	0	0	0	0	0
2	1		E.coli	1	0	10	E.coli	1	0	Meropener	Meropener	Meropener	24	0	0	0	0	0	0
2	1		No growth			1	Enterococc	0	0	Meropener	Piperacillin	Linezolid	14	0	0	0	0	0	0
2	1		No growth			10	Enterococc	0	0	Piperacillin	Linezolid	Linezolid	14	0	0	0	0	0	0
2	1		E.coli	0	1	10	E.coli	0	1	Meropener	Colistin / R	Colistin / R	25	1	0	0	0	0	0
1	1		E.coli	1	0	10	E.coli	1	0	Meropener	Meropener	Meropener	20	0	1	0	0	0	0
2	1		No growth			10	E.coli	1	0	Meropener	Meropener	Meropener	14	0	1	0	0	0	0
2	1		No growth			10	E.coli	1	0	Piperacillin	Ertapenem	Ertapenem	10	0	0	0	0	0	0
2	1		E.coli	1	0	10	E.coli	1	0	Meropener	Meropener	Meropener	7	0	0	0	0	0	0
2	1		No growth			1	E.coli	1	0	Meropener	Meropener	Meropener	14	0	0	0	0	0	0
1	1		No growth			10	E.coli	1	0	Meropener	Meropener	Meropener	14	0	0	0	0	1	0
1	1		E.coli	1	0	10	E.coli	1	0	Meropener	Ertapenem	Ertapenem	14	0	0	0	0	0	0
			E.coli	0	1	10	E.coli	0	1	Meropener	Colistin / N	Colistin / N	14	0	1	0	0	0	0
2	1		No growth			10	Klebsiella	0	0	Piperacillin	ciprofloxac	ciprofloxac	13	0	0	0	0	0	0
2	1		No growth			1	Enterococc	0	0	Piperacillin	Ampicillin	Ampicillin	14	0	0	0	0	0	0
1	1		E.coli	1	1	1	E.coli	1	1	Piperacillin	Colistin / N	Colistin / N	7	0	0	0	0	0	0
1	1		No growth			1	E.coli	1	0	Meropener	Meropener	Meropener	7	0	0	0	0	0	0
2	1		No growth			1	Enterococc	0	0	Meropener	Linezolid	Linezolid	10	0	0	1	0	0	0
2	1		E.coli	0	0	10	E.coli	0	0	Piperacillin	Ciprofloxac	Ciprofloxac	7	0	0	0	0	0	0
2	1		Enterococc	0	0	1	Enterococc	0	0	Meropener	Linezolid	Linezolid	14	0	0	0	0	0	0
1	1		E.coli	1	0	10	E.coli	1	0	Meropener	Meropener	Meropener	14	0	0	0	0	0	0
			E.coli	1	0	1	E.coli	1	0	Meropener	Meropener	Meropener	14	0	0	0	0	0	0
2	1		No growth			10	E.coli	1	0	Meropener	Meropener	Meropener	14	0	0	0	0	0	0
2	1		E.coli	0	0	1	E.coli	0	0	Meropener	Piperacillin	Piperacillin	7	0	0	0	0	0	0
2	1		E.coli	1	0	10	E.coli	1	0	Meropener	Meropener	Meropener	25	1	0	0	0	0	0
2	1		No growth							Piperacillin	Piperacillin	Piperacillin	7	0	0	0	0	0	0
2	1		E.coli	1	0	10	E.coli	1	0	Meropener	Meropener	Meropener	10	0	0	0	0	0	0
1	1		No growth			10	Klebsiella	0	0	Piperacillin	Piperacillin	Piperacillin	7	0	0	0	0	0	0
2	1		E.coli	0	0	10	E.coli	0	0	Piperacillin	Piperacillin	Piperacillin	14	0	0	0	0	0	0
1	1		No growth			10	E.coli	0	0	Piperacillin	Piperacillin	Piperacillin	7	0	0	0	0	0	0
1	1		E.coli	0	0	10	E.coli	0	0	Meropener	Ciprofloxac	Ciprofloxac	6	0	0	0	0	0	0
1	1		No growth							Piperacillin	Piperacillin	Piperacillin	7	0	0	0	0	0	0
2	1		E.coli	0	0	10	E.coli	0	0	Meropener	Amikacin	Amikacin	14	0	0	0	0	0	0
1	1		No growth			10	E.coli	1	0	Meropener	Meropener	Meropener	14	0	0	0	0	0	0
2	1		E.coli	0	0	10	E.coli	0	0	Meropener	Piperacillin	Piperacillin	14	0	0	0	0	0	0
1	1		E.coli	1	0	1	E.coli	1	0	Meropener	Meropener	Meropener	14	0	0	0	0	0	0
1	1		No growth			10	E.coli	1	0	Meropener	Piperacillin	Piperacillin	7	0	0	0	0	0	0
1	1		No growth			1	E.coli	0	0	Meropener	Meropener	Levofloxaci	14	0	0	0	0	0	0
2	1		No growth							Meropener	Meropener	Meropener	14	0	0	0	0	0	0
1	1		No growth			10	E.coli	1	0	Meropener	Meropener	Meropener	7	0	0	0	0	0	0
2	1		No growth							Meropener	Meropener	Meropener	42	0	1	0	0	0	0
2	1		No growth			10	E.coli	1	0	Meropener	Meropener	Meropener	7	0	0	0	0	0	0
2	1		E.coli	1	0	10	E.coli	1	0	Meropener	Meropener	Ertapenem	28	0	0	0	0	1	1
2	1		No growth			10	E.coli	1	0	Piperacillin	Meropener	Meropener	11	0	0	0	0	0	0
2	2		E.coli	1	0	10	Candida	0	0	Meropener	Meropener	Meropener	3	0	0	0	0	0	0
2	1		No growth			1	Staphyloco	0	0	Meropener	Meropener	Meropener	10	0	0	0	0	0	0
1	1		No growth							Meropener	Meropener	Meropener	7	0	0	0	0	0	0
1	1		No growth			10	E.coli	0	0	Meropener	Meropener	Ciprofloxac	7	0	0	0	0	0	0
2	1		E.coli	1	0	10	E.coli	1	0	Meropener	Meropener	Ertapenem	14	0	0	0	0	0	0
2	1		No growth			10	E.coli	0	0	Meropener	Ciprofloxac	Ciprofloxac	4	0	0	0	0	0	0
2	1		Klebsiella	0	0	10	Klebsiella	0	0	Meropener	Ciprofloxac	Ciprofloxac	31	0	1	0	0	1	1
2	1		No growth			10	E.coli	1	0	Meropener	Meropener	Meropener	14	1	1	1	0	0	0
1	1		Klebsiella	0	0	1	Enterococc	0	0	Piperacillin	Piperacillin	Piperacillin	26	1	0	0	0	1	1
2	1		No growth			1	E.coli	1	0	Meropener	Meropener	Meropener	14	0	0	0	0	0	0
2	1		No growth			10	E.coli	0	0	Meropener	Ciprofloxac	Ciprofloxac	3	0	0	0	0	0	0
2	1		E.coli	1	0	1	E.coli	1	0	Piperacillin	Meropener	Meropener	6	0	0	0	0	0	0
2	1		No growth			10	E.coli	0	0	Meropener	Piperacillin	Ciprofloxac	4	0	0	0	0	0	0
2	1		E.coli	1	0	10	E.coli	1	0	Piperacillin	Meropener	Meropener	14	0	0	0	0	0	0
2	1		E.coli	0	0	1	E.coli	0	0	Meropener	Amikacin	Amikacin	14	0	1	0	0	0	0
2	1		E.coli	1	0	10	E.coli	1	1	Meropener	Colistin / N	Colistin / N	14	1	0	0	0	1	0
1	1		No growth			10	E.coli	0	0	Meropener	Ciprofloxac	Ciprofloxac	14	0	0	0	0	0	0
2	1		No growth			10	E.coli	1	0	Meropener	Meropener	Meropener	7	0	0	0	0	0	0
2	1		No growth			10	E.coli	1	0	Meropener	Meropener	Meropener	10	0	0	0	0	0	0
2	1		No growth			1	E.coli	1	0	Meropener	Meropener	Meropener	10	0	0	0	0	0	0
1	1		No growth				Pseudocitro	1	0	Meropener	Meropener	Ertapenem	28	0	1	0	0	0	0
2	1		No growth							Meropener	Meropener	Meropener	7	0	0	0	0	0	0
2	1		E.coli	1	0	10	E.coli	1	0	Meropener	Meropener	Meropener	14	0	0	0	0	0	0
2	1		E.coli	0	0	10	E.coli	0	0	Piperacillin	Piperacillin	Piperacillin	17	0	1	0	0	0	0
2	1		No growth			10	Pseudomor	0	0	Meropener	Meropener	Meropener	3	0	0	0	0	0	0
1	1		E.coli	1	0	10	E.coli	1	0	Meropener	Meropener	Meropener	14	0	0	1	0	0	0
2	1		No growth				Klebsiella	1	0	Meropener	Meropener	Meropener	42	0	1	0	1	0	0
1	1		E.coli	1	0					Piperacillin	Piperacillin	Piperacillin	14	0	0	0	0	0	0
1	1		No growth			10	E.coli	1	0	Ertapenem	Ertapenem	Ertapenem	4	0	0	0	0	0	0
2	1		E.coli	1	0					Piperacillin	Piperacillin	Piperacillin	7	0	0	0	0	0	0
1	1		No growth			10	E.coli	0	0	Meropener	Meropener	Meropener	7	0	0	0	0	0	0
1	1		No growth			10	E.coli	1	0	Piperacillin	Piperacillin	Piperacillin	14	0	1	0	0	1	1
2	1		No growth				Klebsiella /	1	0	Meropener	Meropener	Meropener	14	0	0	0	0	0	0
2	1		E.coli	0	0	10	E.coli	0	0	Meropener	Piperacillin	Piperacillin	14	0	0	0	0	0	0
			E.coli	1	0	10	E.coli	1	0	Meropener	Meropener	Meropener	42	0	1	0	0	1	1
2	2		E.coli	1	0	10	E.coli	1	0	Meropener	Meropener	Meropener	14	0	0	0	0	0	1
2	1		No growth			10	E.coli	0	0	Meropener	Ertapenem	Ertapenem	15	0	0	0	0	0	0
2	1		No growth			1	E.coli	1	0	Meropener	Meropener	Meropener	14	0	0	1	0	0	0
2	1		E.coli	1	0	10	E.coli	1	0	Meropener	Meropener	Meropener	10	0	0	0	0	0	0
2	1		No growth			1	Enterococc	0	0	Meropener	Linezolid	Linezolid	14	0	0	1	0	1	1
2	1		E.coli	1	0	10	E.coli	1	0	Meropener	Meropener	Meropener	27	0	1	0	0	0	0
2	1		No growth			10	E.coli	0	0	Meropener	Piperacillin	Piperacillin	10	0	0	0	0	0	0
2	1		No growth			10	E.coli	1	0	Meropener	Meropener	Meropener	24	1	0	0	0	1	1

surgical	bedcharge	labinvest	noninvas	invastest	drugs	profcharge	pertravel	relative	total	dayfood	relative1	totalfood	dayaccom	relative2	totalaccom	losspay	losswages	moneyarra
0	2775	12240	3475	0	20294	8790	60	2	2980	200	2	3200	0	0	0	0	0	1
0	27528	37332	9430	10305	32174	8200	150	2	1140	300	2	660	0	0	0	0	0	1
0	37370	52039	11445	0	62864	62864	80	2	1040	0	0	0	0	0	0	0	0	1
0	13910	10240	2405	0	17324	4550	150	2	1950	100	2	2600	0	0	0	0	0	2
0	50011	69850	1935	3185	11080	10250	120	2	240	100	2	3000	0	0	0	0	0	1
0	8800	7977	1655	0	18948	2800	420	2	700	100	2	2400	0	0	0	0	0	1
0	16050	13888	3070	0	19483	5250	250	2	3000	0	0	0	0	0	0	0	0	1
0	12210	15267	2560	0	9371	3850	700	2	2350	60	2	1320	0	0	0	0	0	2
0	21400	24300	9200	0	18922	7000	130	2	900	100	2	4000	0	0	0	0	0	2
0	26750	32450	8620	0	113954	8750	150	2	3300	250	2	7250	0	0	0	0	10000	1
0	30880	120829	12460	0	29204	28640	2500	2	6500	100	2	2400	0	0	0	0	0	1
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education	marital	ill	wrnghealth	quality	satihealth	phypain	medtreat	enjoylife	meaningful	concent	safelife	environ	everyday	appearanc	money	daytoday	leisure	getaround
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sleep	ability	capacity	yourself	personal	sexlife	friends	liveplace	healthser	transport	negfeel	help	domain1	domain2	domain3	domain4	scaled1	scaled2	scaled3	scaled4
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4	4	4	4	4	3	4	4	4	4	2	1	26	15	11	28	67.86	37.5	66.67	62.5
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2	2	2	2	2	3	2	2	2	2	2	1	18	12	7	17	39.29	25	33.33	28.13
3	2	2	2	2	3	4	3	4	4	2	1	20	13	9	25	46.43	29.17	50	53.13
3	3	3	3	3	3	3	3	3	3	3	1	20	18	9	24	46.43	50	50	50
2	2	2	1	2	3	4	4	4	4	3	1	18	12	9	22	39.29	25	50	43.75
1	2	2	2	2	3	4	3	3	3	3	1	17	13	9	19	35.71	29.17	50	34.38
3	3	3	4	4	4	4	4	4	4	4	1	23	20	12	28	57.14	58.33	75	62.5
4	4	4	4	4	3	4	4	4	4	4	1	25	17	11	27	64.29	45.83	66.67	59.38
2	2	2	2	4	3	4	3	3	3	3	1	18	13	11	20	39.29	29.17	66.67	37.5
2	2	2	2	2	3	2	2	3	3	2	1	18	12	7	18	39.29	25	33.33	31.25
4	4	4	4	4	3	4	4	4	4	5	1	24	19	11	24	60.71	54.17	66.67	50
2	2	2	2	2	2	2	3	2	2	4	1	19	15	6	17	42.86	37.5	25	28.13
2	2	2	2	2	3	2	3	3	3	4	1	20	18	7	19	46.43	50	33.33	34.38
3	4	3	3	4	3	4	4	4	3	4	1	23	18	11	22	57.14	50	66.67	43.75
4	4	3	4	4	3	4	4	2	2	4	1	23	19	11	22	57.14	54.17	66.67	43.75
2	3	3	4	4	3	4	4	4	4	4	1	20	20	11	24	46.43	58.33	66.67	50
2	1	1	3	3	3	4	4	4	3	5	1	15	16	10	21	28.57	41.67	58.33	40.63
3	3	3	3	3	3	3	3	3	3	2	1	21	16	9	22	50	41.67	50	43.75
2	3	3	2	3	3	3	3	3	3	2	1	20	17	9	22	46.43	45.83	50	43.75
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2	3	3	4	2	3	2	2	3	3	3	1	20	16	7	20	46.43	41.67	33.33	37.5
3	3	3	2	3	3	4	4	3	3	4	1	21	17	10	25	50	45.83	58.33	53.13
2	3	3	2	2	3	3	3	4	3	4	1	21	15	8	21	50	37.5	41.67	40.63
3	3	3	2	2	3	2	2	2	3	5	1	23	16	7	22	57.14	41.67	33.33	43.75
2	3	2	2	3	3	3	2	2	3	5	1	18	15	9	21	39.29	37.5	50	40.63
2	2	2	3	3	3	3	2	3	3	4	1	17	16	9	19	35.71	41.67	50	34.38
2	2	2	2	2	3	3	2	3	3	4	1	17	16	8	21	35.71	41.67	41.67	40.63
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2	2	2	2	2	3	4	4	4	3	4	1	17	17	9	21	35.71	45.83	50	40.63
4	4	3	4	3	3	4	4	4	3	4	1	27	18	10	22	71.43	50	58.33	43.75
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4	4	4	4	4	3	4	4	4	3	5	1	28	21	11	28	75	62.5	66.67	62.5
2	2	2	2	3	3	2	2	2	2	4	1	20	18	8	19	46.43	50	41.67	34.38
2	2	2	2	2	3	2	2	3	3	2	1	18	12	7	18	39.29	25	33.33	31.25
2	3	3	2	3	3	4	4	4	4	2	1	19	13	10	24	42.86	29.17	58.33	50
2	2	2	3	3	3	3	3	3	3	3	1	19	14	9	19	42.86	33.33	50	34.38
3	3	3	3	3	3	3	3	3	2	4	1	21	17	9	19	50	45.83	50	34.38
2	4	4	3	3	3	4	4	3	3	4	1	25	17	10	23	64.29	45.83	58.33	46.88
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4	4	4	4	4	3	4	3	3	3	3	0	24	17	11	24	60.71	45.83	66.67	50
2	2	2	2	2	3	2	2	2	3	4	1	16	17	7	19	32.14	45.83	33.33	34.38
2	1	1	1	4	3	4	4	4	3	3	1	14	12	11	20	25	25	66.67	37.5
4	4	4	4	4	3	4	4	3	3	4	1	25	20	11	23	64.29	58.33	66.67	46.88
4	4	4	3	3	3	4	4	4	3	3	1	24	17	10	24	60.71	45.83	58.33	50
4	3	2	3	4	3	4	4	4	4	4	1	17	16	11	25	35.71	41.67	66.67	53.13
4	4	3	4	4	3	3	4	5	5	4	1	24	17	10	32	60.71	45.83	58.33	75
2	3	2	2	2	3	3	3	3	3	4	1	19	15	8	20	42.86	37.5	41.67	37.5
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2	2	2	3	2	3	2	3	2	2	4	1	19	15	7	17	42.86	37.5	33.33	28.13
2	2	2	4	4	3	4	4	4	4	5	1	19	21	11	31	42.86	62.5	66.67	71.88
2	2	2	2	2	3	3	2	2	2	4	1	18	16	8	16	39.29	41.67	41.67	25
2	2	2	2	2	3	2	2	2	2	2	1	18	12	7	16	39.29	25	33.33	25
4	4	2	4	3	3	4	4	3	2	4	1	24	17	10	20	60.71	45.83	58.33	37.5
2	3	3	3	3	3	4	3	3	3	3	1	19	16	10	24	42.86	41.67	58.33	50
3	2	2	2	2	3	4	4	4	3	4	1	21	17	9	28	50	45.83	50	62.5
2	2	2	2	2	3	2	2	3	3	3	1	17	13	7	19	35.71	29.17	33.33	34.38
2	2	2	3	3	3	4	2	2	4	2	1	17	14	10	22	35.71	33.33	58.33	43.75
2	3	3	3	2	3	3	3	3	3	3	1	21	14	8	20	50	33.33	41.67	37.5
2	2	3	2	2	2	2	2	2	2	4	1	19	14	6	16	42.86	33.33	25	25
2	2	4	2	4	3	4	4	4	4	4	1	22	20	11	31	53.57	58.33	66.67	71.88
2	2	2	2	2	3	2	2	2	2	4	1	18	14	7	17	39.29	33.33	33.33	28.13
3	3	3	3	3	3	4	3	3	2	5	1	21	20	10	20	50	58.33	58.33	37.5
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2	2	2	3	3	3	2	3	3	3	4	1	20	15	8	21	46.43	37.5	41.67	40.63
2	2	2	2	2	3	2	2	2	3	4	1	18	14	7	18	39.29	33.33	33.33	31.25
4	3	3	4	4	3	3	4	4	4	5	1	27	19	10	28	71.43	54.17	58.33	62.5
2	2	2	2	2	3	4	4	2	2	4	1	17	13	9	18	35.71	29.17	50	31.25
2	2	2	2	2	3	4	2	2	3	3	1	17	14	9	17	35.71	33.33	50	28.13
2	2	2	2	2	3	4	4	4	4	3	1	18	13	9	22	39.29	29.17	50	43.75
2	2	2	2	2	3	2	2	2	2	4	1	18	14	7	17	39.29	33.33	33.33	28.13
3	3	4	3	3	3	4	3	3	3	4	1	23	20	10	26	57.14	58.33	58.33	56.25
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2	2	2	2	2	2	2	2	2	2	4	1	19	15	6	17	42.86	37.5	25	28.13
2	2	2	2	2	2	2	2	2	2	4	1	17	14	6	16	35.71	33.33	25	25
1	2	2	3	2	3	3	2	3	2	4	1	18	16	8	17	39.29	41.67	41.67	28.13
3	3	3	3	3	3	4	4	4	4	5	1	21	20	10	26	50	58.33	58.33	56.25
2	2	2	2	2	3	2	2	2	2	4	1	18	14	7	16	39.29	33.33	33.33	25
3	3	3	3	3	3	3	3	3	3	3	1	22	14	9	19	53.57	33.33	50	34.38
5	5	5	5	4	3	5	5	5	5	5	1	28	18	12	25	75	50	75	53.13
2	2	2	2	2	3	4	4	4	5	4	1	19	14	9	29	42.86	33.33	50	65.63
2	2	3	3	3	3	4	4	3	4	4	1	20	15	10	22	46.43	37.5	58.33	43.75
2	3	2	3	4	3	4	4	4	4	4	1	19	17	11	27	42.86	45.83	66.67	59.38
4	2	2	2	3	3	4	4	4	3	3	1	20	9	10	21	46.43	12.5	58.33	40.63
2	2	1	1	3	1	4	4	5	4	2	1	9	8	8	26	7.14	8.33	41.67	56.25
2	3	3	2	3	3	4	4	4	4	4	1	20	14	10	22	46.43	33.33	58.33	43.75

APPENDIX- 9 CHEERS checklist

CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force*, provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis"], and describe the interventions compared.	1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	99
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	1,2
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	44
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	44
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	45,46,47
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	45,46
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	44
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	47
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	49
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	46-50

	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	49
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	44
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	45-47
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	45-47
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	45-47
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	46,48,51
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	49,50
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	49,50
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	51-56
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	57-61
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	47

		of methodological assumptions (such as discount rate, study perspective).	47
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	52-55
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	57,59
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	68-72
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	50
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	None

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

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