Evidence of the impact of kidney disease on Drug Metabolism and Transport

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Problems with drug administration in CRF

- Numerous drugs to treat co-morbid conditions in CRF patients
- Important incidence of side-effects associated with high morbidity
- Secondary to inadequate dosage

Repercussions of CRF on pharmacokinetics of drugs

- Despite the adjustment of dosage in function of glomerular filtration, there is an accumulation of several drugs that could only be explained by a decrease in their non-renal clearance
  - **Metabolism**
  - **Transport**

Repercussions of CRF on non-renal clearance of drugs

Drug Substrate	Renal Function	f_e	CL_T	CL_R	CL_{NR}	$\%\Delta CL_{NR}$*	AUC	$t_{1/2}$ (hr)	CL_{NR} Pathway(s)
Bupropion[27]	Normal	0.5	414 L/hr	NR	NR		0.49 μg·hr/mL	8.1	CYP2B6
	CKD		155	NR	NR		1.1	19.4	
Cerivastatin[28]	Normal	0	22.2 L/hr	NR	NR		13.5 μg·hr/L	2.3	CYP2C8, CYP3A4, P-gp, OATP, MRP, BCRP
	CKD		13.3	NR	NR		22.5	3.4	
Cibenzoline[29]	Normal	43	707 mL/min	344	363		1905 ng·hr/mL	7.3	CYP2D6, CYP3A4
48-hr interdialytic period	ESRD		224	0	224	-38	6646	22.4	
Cyclophosphamide[30]	Normal	19	79 mL/min	14.9	64.1			4.8	CYP2B6, CYP2C9, CYP3A4, MRP, BCRP
	CKD		47	2.4	44.6	-30	+77%*	7.3	
Erythromycin[31]	Normal	5	4,052 mL/min	NR	NR		4.7 mg·hr/L	2.1	CYP3A4, P-gp, OATP
Non-dialysis day	ESRD		1,147	NR	NR		20.1	2.7	
Felbamate[32]	Normal	30	0.50 mL/min/kg	0.15	0.35		526 μg·hr/mL	19.2	CYP2E1, CYP3A4
	CKD		0.25	0.02	0.23	-34	1119	33.9	
Lidocaine[33]	Normal	<5	11.0 mL/min/1.73 m^2	NR	NR		NR	2.2	CYP1A2, CYP3A4
	CKD		6.0	NR	NR		NR	4.6	
Non-dialysis day	ESRD		11.1	NR	NR		NR	2.6	

Clin Pharmacol Ther 83:898, 2008

Plan

- Repercussions of CRF on nonrenal clairance of drugs in animals and human
  - Metabolism
  - Transport
- Administration of drugs in CRF
- New recommendations
  - FDA
  - KDIGO

Cytochrome P450 (Phase I)

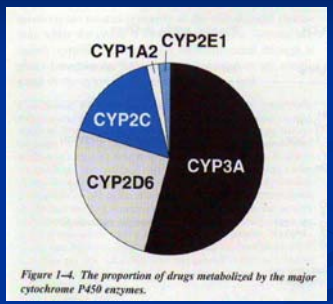


Figure 1–4. The proportion of drugs metabolized by the major cytochrome P450 enzymes.

Conjugaison reactions (phase II)

- Glucuronidation
- Acétylation
- Sulfonation (sulfation)
- Methylation
- Glutathione
- Acides aminés

Animal model : 5/6 nephrectomy

Physiological characteristics of the animal model

	Control	CRF
Weigth (g)	310 ± 10	308 ± 23
Creatinine (umol/L)	57 ± 3	154 ± 12[a]
Urea (mmol/L)	5.6 ± 0.7	26. ± 3.9[a]
Clearance (mL/min)	0.88 ± 0.5	0.33 ± 0.03[a]

[a] $p < 0.001$

JASN 12:326, 2001

Alterations in liver metabolic enzymes in CRF rats

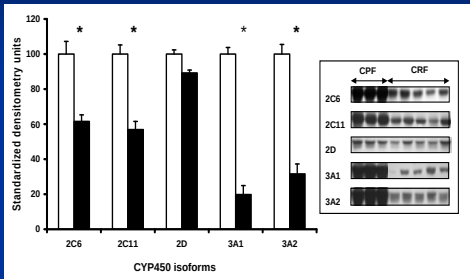
	Liver			
	Protein	*RNA*	*Activity*	*Effect*
Metabolic Enzymes				
CYP1A1	↔	↔	↔	↔ metabolic CL
CYP2B1	NA	NA	NA	NA
CYP2C6	NA	NA	NA	NA
CYP2C11	↓ 45%	↓	↓ 35%	↓ metabolic CL
CYP2D	↔	↔	NA	↔ metabolic CL
CYP3A1	↓ 85%	↓	↓ 35%	↓ metabolic CL
CYP3A2	↓ 45%	↓	↓ 35%	↓ metabolic CL
Nat1	↓ 33%	NA	↓ 45%	↓ metabolic CL
Nat2	↓ 50%	↓ 35%	↓ 50%	↓ metabolic CL

Clin Pharmacol Ther 83:898, 2008

Mechanism of drug enzymes down-regulation in CRF

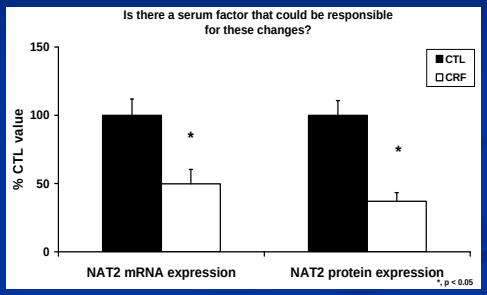
- Circulating factors in uremia

Down-regulation of liver P450: role of uremic mediators



BJP 137:1039, 2002

Effect of CRF on hepatic N-acetyltransferases

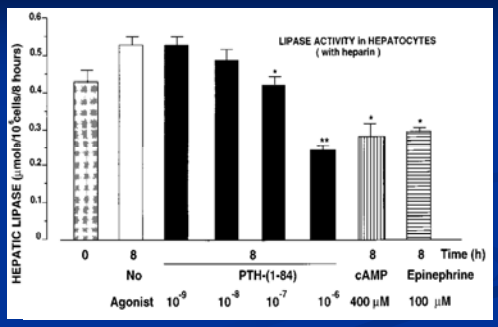


JASN 19:1352, 2008

Which circulating factor ?

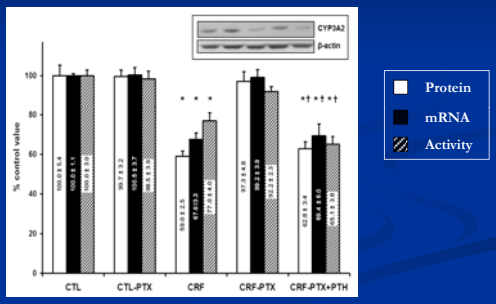
- Several uremic toxins accumulate in CRF
- CRF is a state of chronic inflammation : cytokines
- CRF is associated with numerous metabolic disturbances
  - Secondary hyperparathyroidism: elevated parathyroid hormone (PTH)

Effect of PTH on liver protein activity



J Clin Invest 97:2167, 1996

Does PTH depletion by parathyroidectomy in CRF rats prevent the downregulation of P450 3A *in vitro*?



JASN 17:3041, 2006

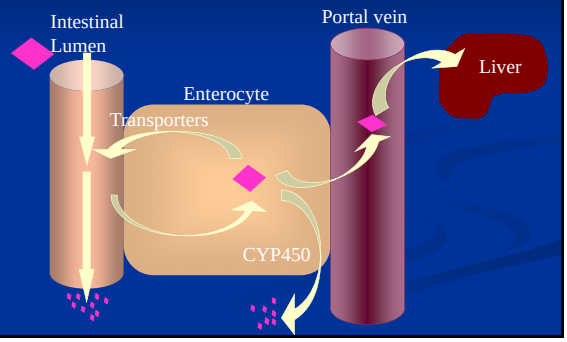
Repercussions of CRF on drug metabolism

- CRF could decrease the metabolism of drugs
  - In the liver
  - In the intestine

Repercussions of CRF on intestinal metabolism of drugs

- Phase I enzymes are present in the intestine
- The intestine is implicated in drug metabolism
  - First-pass metabolism
  - Systemic metabolism

Bioavailability of drugs: intestinal first pass metabolism and drug extrusion



Alterations in intestinal metabolic enzymes in CRF rats

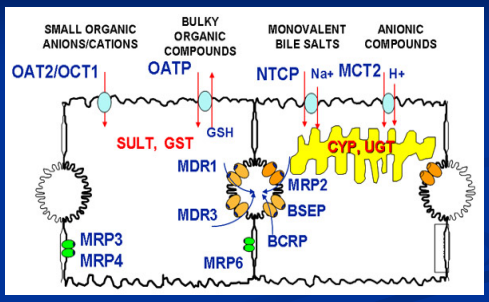
	Intestine			
	Protein	*RNA*	*Activity*	*Effect on bioavailability*
Metabolic Enzymes				
CYP1A1	↓ 40%	↓ 32%	↓ 25%	↑
CYP2B1	↔	↔	NA	↔
CYP2C6	↔	↔	NA	↔
CYP2C11	↔	↔	NA	↔
CYP2D	NA	NA	NA	NA
CYP3A1	NA	NA	NA	NA
CYP3A2	↓ 70%	↓ 36%	↓ 25%	↑
Nat1	NA	NA	NA	NA
Nat2	NA	NA	NA	NA

Clin Pharmacol Ther 83:898, 2008

Repercussions of CRF on drug transport

- CRF could decrease the transport of drugs
  - In the liver
  - In the intestine

Decreased drug liver uptake in CRF



Alterations in liver drug transporters in CRF rats

	Liver			
	Protein	*RNA*	*Activity*	*Effect*
Transporters				
P-gp	↑ 20%	↑ 50%	↑ 45%	↑ biliary excretion
MRP2	↔	↑ 40%	NA	↔ biliary excretion
MRP3	NA	NA	NA	NA
Oatp2	↓ 40%	↔	NA	↓ metabolic CL ↓ biliary excretion
Oatp3	NA	NA	NA	NA

Clin Pharmacol Ther 83:898, 2008

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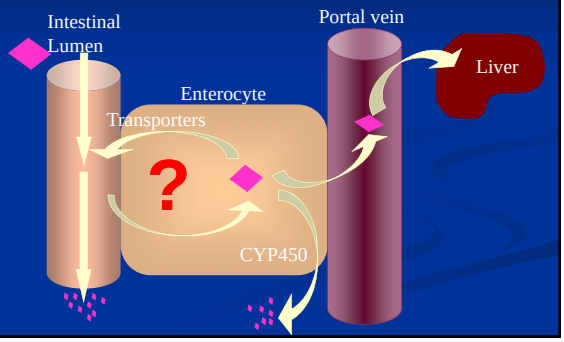
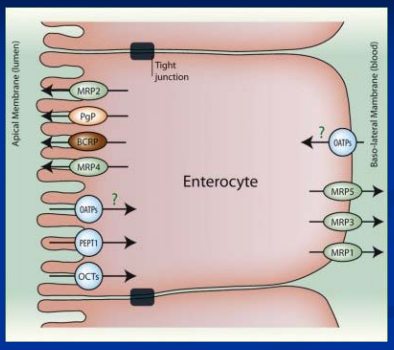


Intestinal drug transporters



Alterations in intestinal transporters in CRF rats

	Intestine			
	Protein	*RNA*	*Activity*	*Effect on bioavailability*
Transporters				
P-gp	↓ 65%	↔	↓ 60%	↑
MRP2	↓ 60%	↔	↓ 35%	↑
MRP3	↓ 35%	NA	NA	↓
Oatp2	↔	NA	NA	↔
Oatp3	↔	↔	NA	↔

Clin Pharmacol Ther 83:898, 2008

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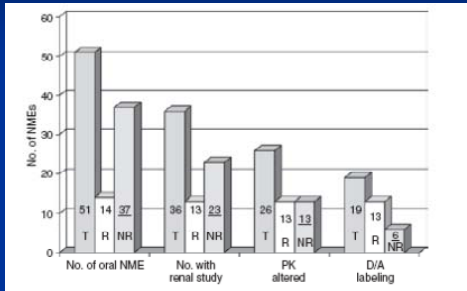
Clin Pharmacol Ther 83:898, 2008

Oral NMEs with renal impairment studies (2003-2007)



Clin Pharmacol Ther 85:305, 2009

Oral NMEs with renal impairment studies (2003-2007)

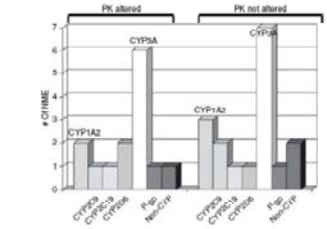


Figure 2 Distribution of enzymes and transporters grouped by pharmacokinetic outcomes in renal impairment for nonrenally eliminated new molecular entities (NMEs). PK, pharmacokinetics.

Clin Pharmacol Ther 85:305, 2009

Drug metabolism and transport in CRF patients

- Indirect data (pharmacokinetic studies)
- *In vitro* studies
- *In vivo* studies

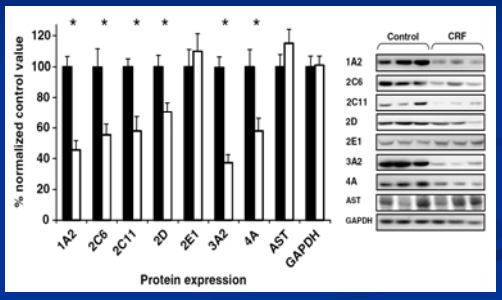
Downregulation of liver P450: role of uremic mediators

Table 1 Characteristics of the CRF patients

	Etiology of CRF	*Age*	*Gender*	*GFR*
Patient 1	Diabetes	65	M	11.7
Patient 2	Ischemic	66	M	8.6
Patient 3*	Ischemic	75	M	7.6
Patient 4	Obstructive	74	M	9.5
Patient 5*	Glomerulonephritis	68	M	7.7
Patient 6	Ischemic	30	F	1.6
Patient 7	Diabetes	73	F	6.9
Patient 8	FSGS	35	F	4.8
Patient 9	Hypertension	75	F	6.6
Patient 10	Diabetes	70	F	3.9
Patient 11	Diabetes	64	M	8.8
Patient 12	Hypertension	59	M	5.0
Patient 13	Diabetes	49	M	5.4
Patient 14	Glomerulonephritis	58	F	5.2
Patient 15	Diabetes	58	F	11.5
Patient 16	Diabetes	39	F	9.0

BJP, 144:1067, 2005

Downregulation of liver P450: role of uremic mediators



BJP, 144:1067, 2005

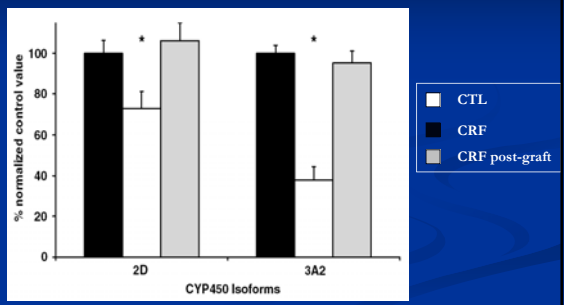
Down-regulation of liver P450: role of uremic mediators

Table 3 Characteristics of the CRF patients with kidney transplantation

	Etiology of CRF	*GFR before dialysis* (ml min^{-1} 1.73 m^{-2})	*Time on dialysis* (months)	*Time after transplantation* (days)	*GFR after transplantation* (ml min^{-1} 1.73 m^{-2})
Patient 21	Alport	5.7	10	32	37.5
Patient 23	Pyelonephritis	6.6	12	63	33.1
Patient 25	Glomerulonephritis	10.2	26	59	109.6
Patient 26	Polycystic	5.5	10	34	53.9
Patient 27	Diabetes	8.4	5	62	69.4
Patient 28*	FSGS	5.6	27	31	59.9
Patient 29	IgA	6.2	18	47	28.6
Patient 30	Diabetes	7.9	15	38	71.3

BJP, 144:1067, 2005

Downregulation of liver P450: role of uremic mediators



BJP, 144:1067, 2005

Drug metabolism and transport in CRF patients

- Indirect data (pharmacokinetic studies)
- *In vitro* studies
- *In vivo* studies

CYP2C9 activity in end-stage renal disease

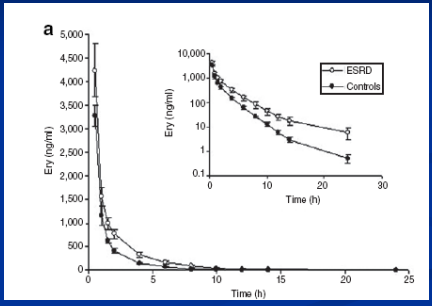
Table I. Demographic characteristics, warfarin requirements, INR, and plasma *S/R* ratio in *CYP2C9*1/*1* ESRD patients and control subjects

Characteristic	ESRD patients	Control subjects	P value
No.	7	6	—
Gender (female/male)	2/5	4/2	—
Race (black/white)	7/0	2/4	—
Age (y)*	45.9 ± 10.3	63.3 ± 13.0	<.02
Warfarin (mg/d)*	4.9 ± 1.5	6.2 ± 3.1	NS
INR*	2.05 ± 1.28	2.37 ± 0.49	NS
Plasma *S/R* ratio*	0.82 ± 0.25	0.55 ± 0.09	<.03

INR, International normalized ratio; ESRD, end-stage renal disease; NS, not significant.
*Presented as mean ± SD.

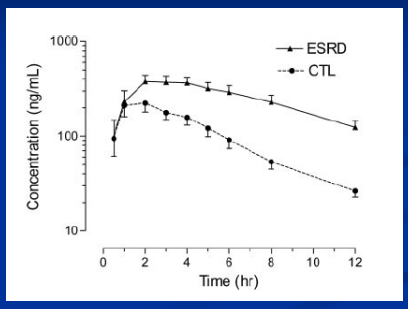
Clin Pharmacol Ther 73:475, 2003

Hepatic clearance of erythromycin is altered in ESRD patients



Clin Pharmacol Ther 87:465, 2010

ESRD impairs non-renal clearance of fexofenadine



JASN 20:2269, 2009

Non-renal clearance of midazolam in ESRD patients

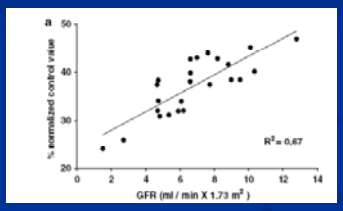
Table 2. Pharmacokinetic parameter estimates of midazolam and 1′-hydroxymidazolam after oral administration of midazolam 2 mg

Parameter	Control Subjects	Patients with ESRD	P
Midazolam			
C_{max} (ng/ml; mean ± SD)	12.3 ± 3.9	11.0 ± 5.3	NS
t_{max} (h; median [range])	0.50 (0.33 to 0.75)	0.50 (0.33 to 1.50)	NS
$t_{1/2}$ (h; mean ± SD)	1.8 ± 0.7	2.4 ± 2.4	NS
CL/F (L/h; mean ± SD)	88.9 ± 24.6	96.9 ± 46.8	NS
$AUC_{0\ to\ \infty}$ (h*ng per ml; mean ± SD)	23.8 ± 5.7	26.1 ± 13.9	NS
1′-Hydroxymidazolam			
C_{max} (ng/ml; mean ± SD)	3.6 ± 1.5	3.0 ± 1.3	NS
t_{max} (h; median [range])	0.750 (0.330 to 0.750)	0.625 (0.330 to 1.500)	NS
$AUC_{0\ to\ \infty}$ (h*ng per ml; mean ± SD)	6.4 ± 2.5	6.5 ± 2.3	NS

JASN 20:2269, 2009

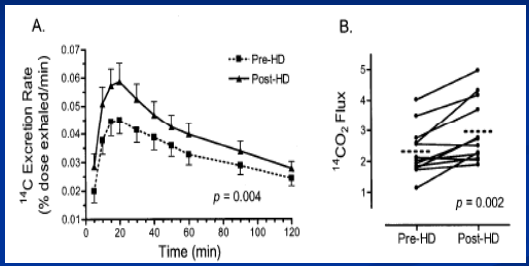
Why discrepancies between animal an human ?

- The severity of renal failure



- Dialysis

Effects of hemodialysis



JASN 17:2363, 2006

Plan

- Repercussions of CRF on nonrenal clairance of drugs in animals and human
  - Metabolism
  - Transport
- Administration of drugs in CRF
- New recommendations

What are the strategies to prevent the accumulation of drugs in CRF patients?

- Dose adaptation to obtain identical C_{max} and AUC
- Theoritically:
  - Increase the interval only
  - Decrease the dose only
  - Both

Repercussions of CKD on kinetics of drugs

Factors involved in PK	Kidney disease effects	Measured specifically for incorporation into drug dosage
Absorption	+	N
Intestinal and first pass metabolism	+	N
Distribution	++	N
Clearance		
Renal	+++	Y
Nonrenal	++	N

Plan

- Repercussions of CRF on nonrenal clairance of drugs in animals and human
  - Metabolism
  - Transport
- Administration of drugs in CRF
- New recommendations

2010 Draft Renal Guidance

- Published for public comments: March 2010 -


Guidance for Industry

Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling

DRAFT GUIDANCE

An update of the 1998 guidance


Guidance for Industry

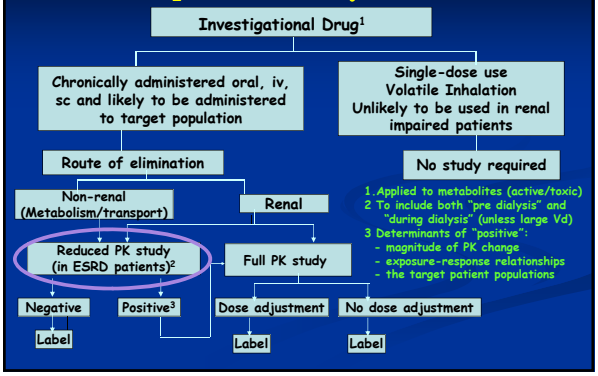
Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.htm

Modifications 1998-2010

- PK studies for nonrenal clearance drugs
- Use of eGFR (MDRD), as well as Clcr (Cockcroft-Gault)
- PK studies in hemodialysis (per et interdialytic)

Figure 1. Decision tree to determine when a renal impairment study is recommended



Modifications 1998-2010

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GFR evaluation

- The diagnosis of renal failure (and its classifiaction)
  - MDRD (ou CKD-EPI)
- The majority of PK data in CRF patients
  - Cockcroft-Gault (C-G)

AJKD 54:33-42, 2009

Table 3

Concordance between kidney function categories assigned using measured GFR vs. estimated kidney function

Equation	Concordant (%)*	Discordant (%)	
		Lower than mGFR	Higher than mGFR
MDRD Study	78	14	8
CG	73	12	16
CG_{IBW}	66	29	5

* p-value <0.001 for the difference in concordance among all equations

Abbreviations: mGFR, measured glomerular filtration rate; MDRD, Modification of Diet in Renal Disease Study equation; CG, Cockcroft-Gault equation using actual body weight; CG_{IBW}, Cockcroft-Gault equation using ideal body weight.

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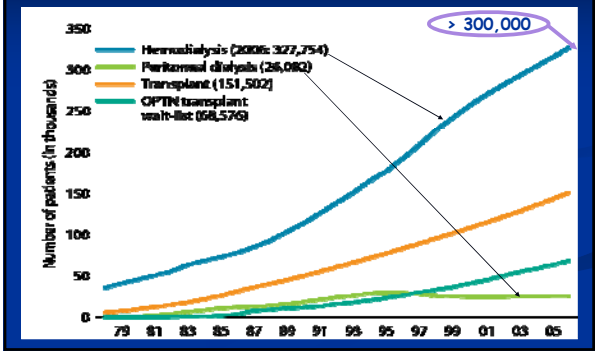
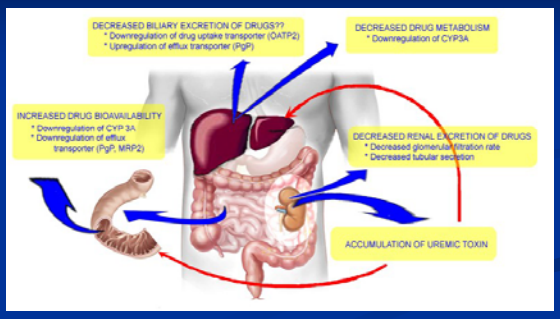
Prevalent Patient Counts (USRDS)- by Modality



Conclusions



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