

Drug Prescribing in Kidney Disease: Initiative for Improved Dosing

Drug Dosing in Patients with Multiple Organ Dysfunction

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Kidney Disease: Improving Global Outcomes

Areas for Consideration

- Patients
- Phases of disease
- Process of care
- Organ interactions
- Factors influencing drug disposition and drug dosing
- Questions to be addressed



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Areas for Consideration

1. Patients

- Multiple Organ Dysfunction Syndrome – Acute
 - Altered organ function in acutely ill patients *e.g. Traumatic brain injury in a 20 yr old previously healthy adult.*
- Multiple System Organ Failure – Acute on Chronic disease
 - Altered organ function with pre-existing co-morbidities *e.g. pneumonia in 45 yr old patient with multiple sclerosis*
- Multiple Organ Dysfunction Syndrome – Chronic
 - Altered organ function secondary to multimorbidity *e.g. 55 yr old obese patient with diabetes, hypertension, Hep C cirrhosis and aortic stenosis*

Clinical practice guidelines rarely account for patients with multiple chronic conditions (JAMA 2010;303:1303-4)

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Epidemiology

- As many as 19% of ICU patients develop MODS
- MODS is responsible for 50%–80% of ICU deaths.
- Patients who develop MODS have a 20-fold increase in mortality rate and a doubled length of stay (LOS) compared with unaffected patients.
- Moreover, MODS is the most common diagnosis in ICU patients with a long LOS (>21 days) .

Mizock BA Dis Mon 2009;55:476-526

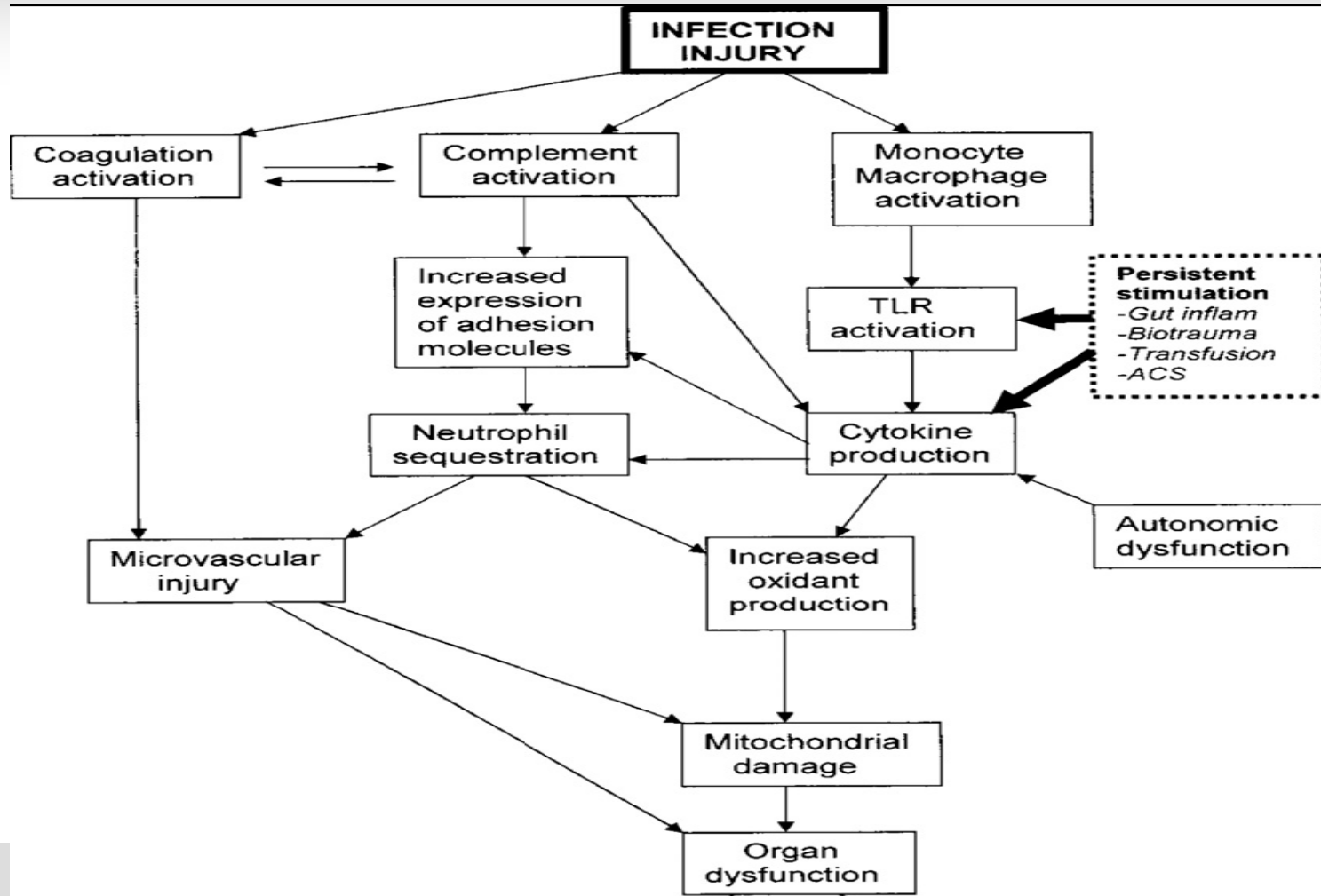
Barie PSSurgical Infections ;10:2009

Proulx F, et al Pediatr Crit Care Med 2009;10:12-22

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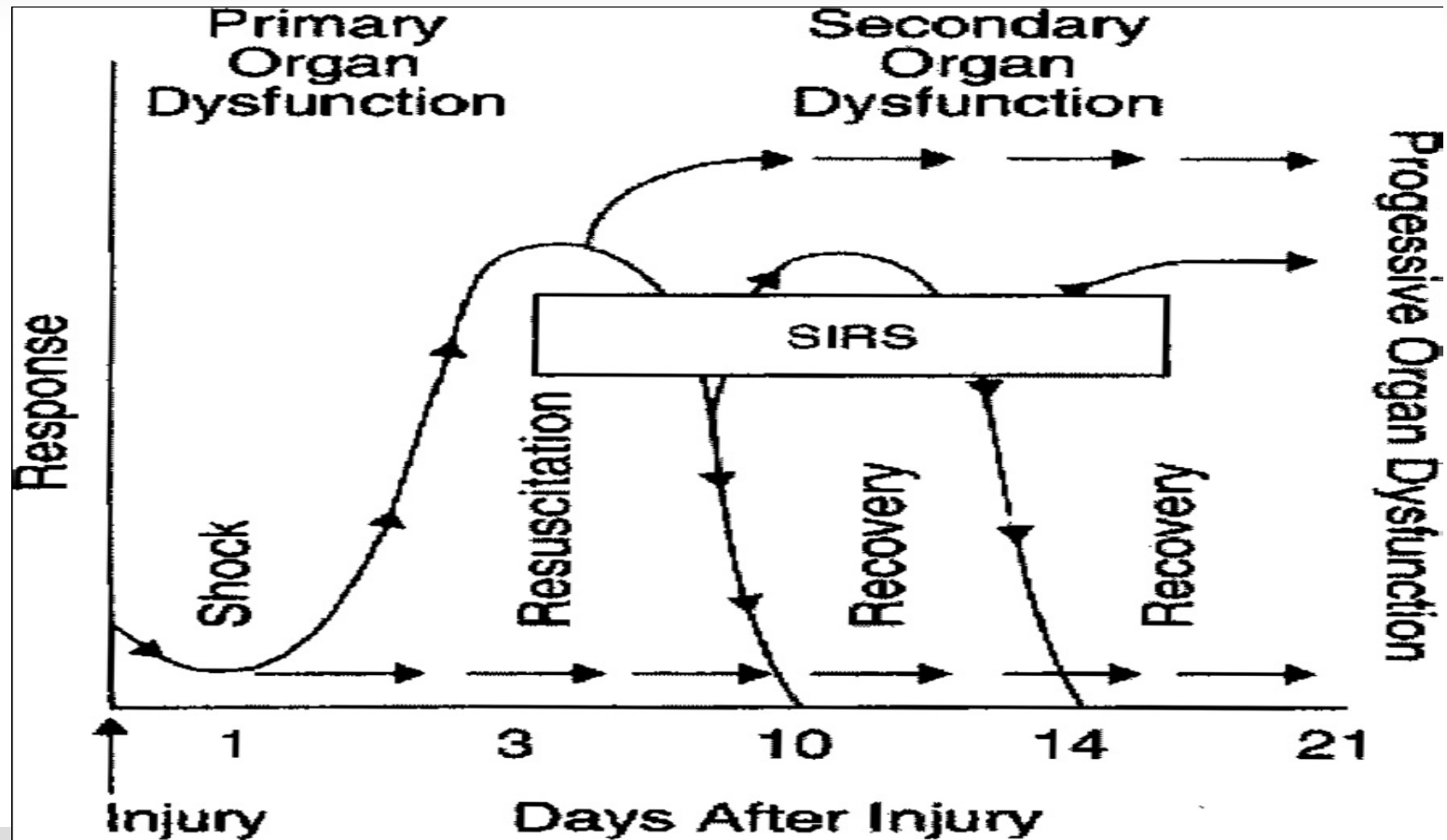
Inflammation is a common feature of MODS



Mizock BA Dis Mon 2009;55:476-526

Areas for Consideration

2. Phases of disease



Areas for Consideration

3. Process of Care

- Fluid resuscitation
- Tissue perfusion
 - pressors,
 - vasodilators and inotropes
- Nutritional support
- Mechanical Ventilation
- Organ specific interventions e.g. hypothermia for stroke
- RRT
- Other support modalities e.g. ECMO



Fluid accumulation is common secondary to resuscitation procedures

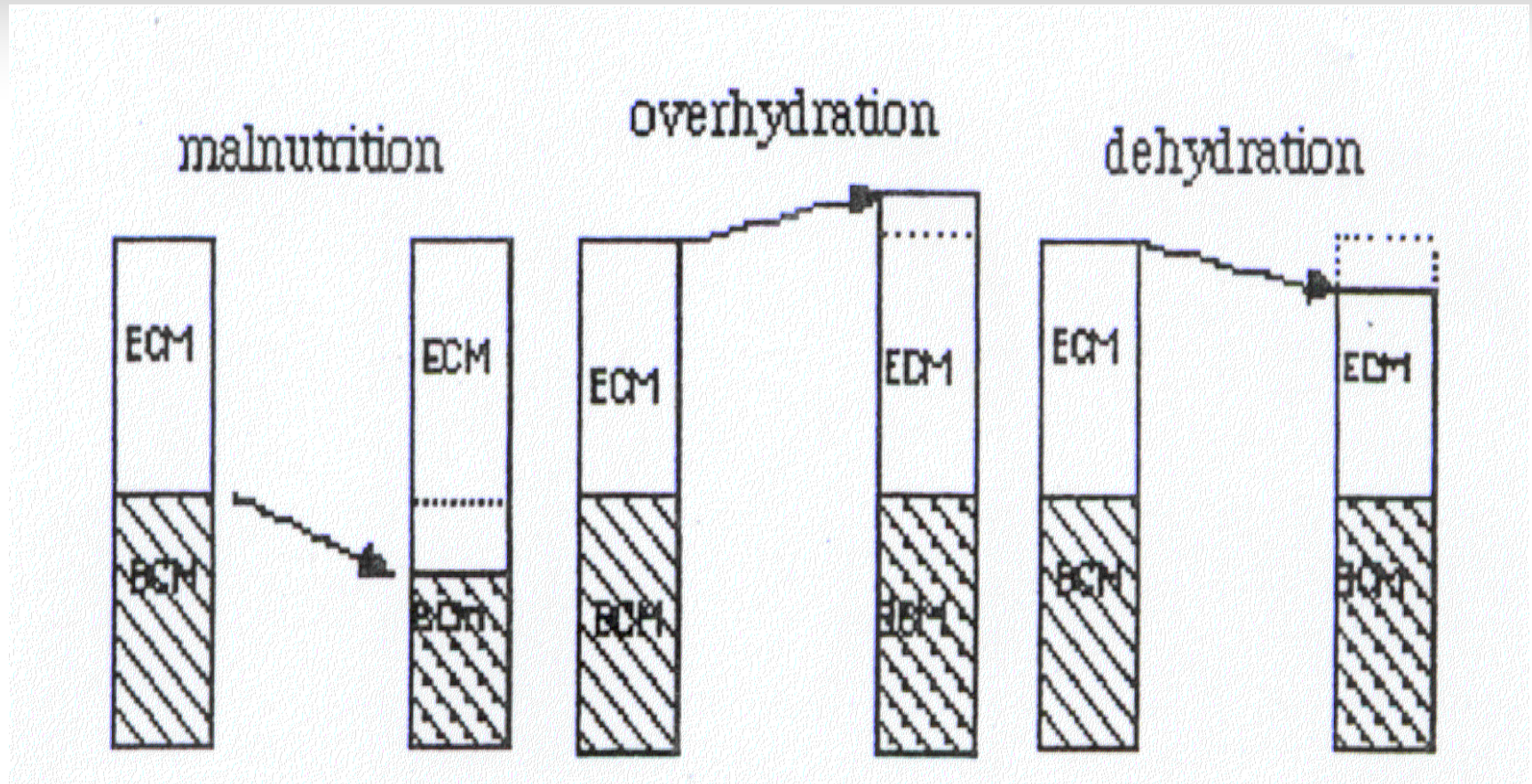
- Sodium and water over load may be an inevitable consequence of the resuscitation process.
- Septic patients in the ICU gain as much as 12.5 L of body water during the first two days of resuscitation.
- It may take up to 3 weeks for patients to excrete this excess load.



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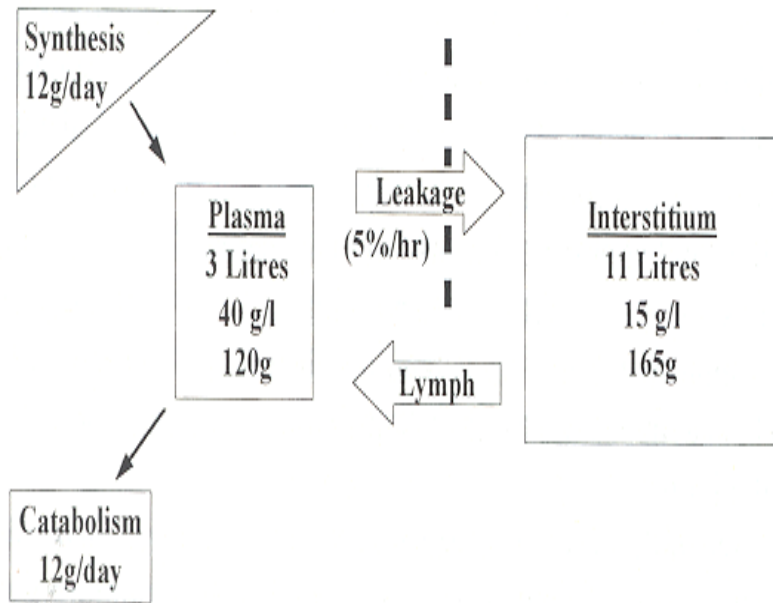
Plank *et al*, Ann Surg 1998

Body Compartment Alterations are Common

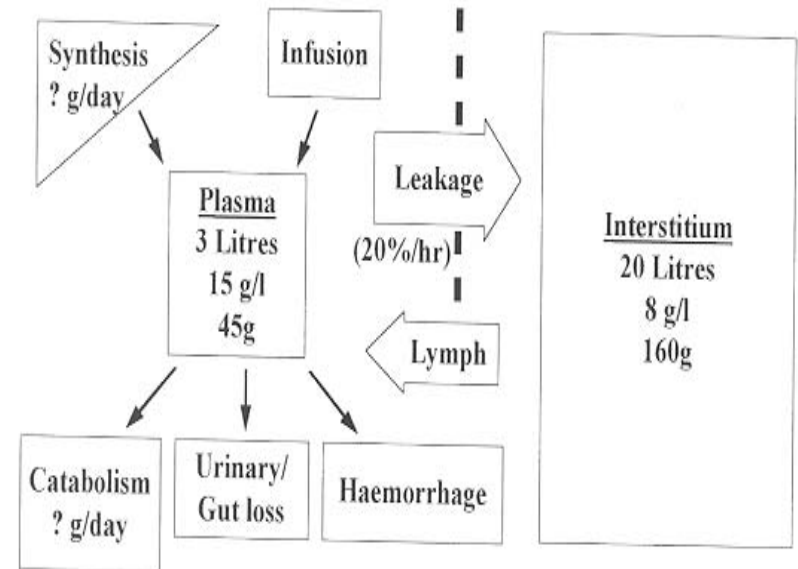


Albumin Pharmacokinetics

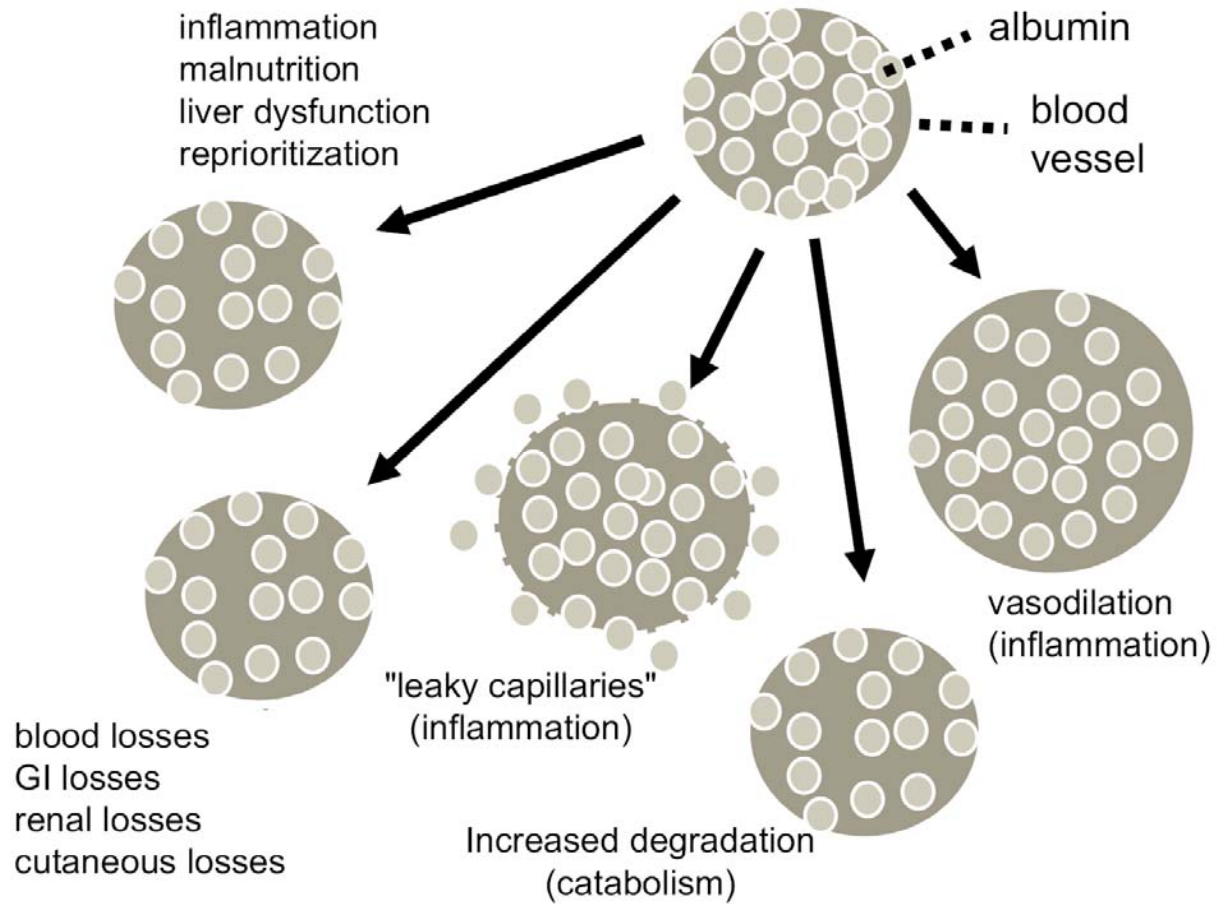
Normal



Critical Illness

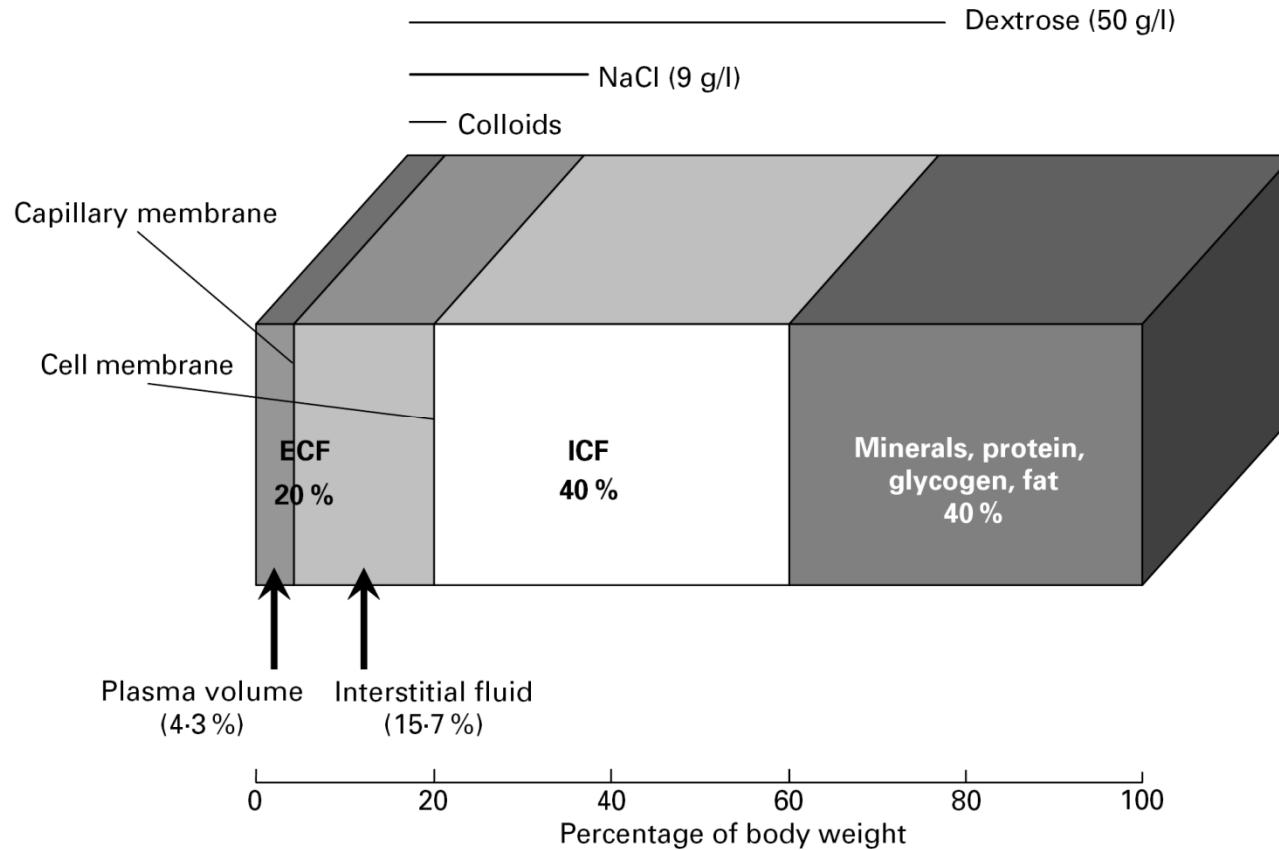


Hypoalbuminemia in Critically Ill Patients



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Response to Fluid Administration



Distribution of infused fluids (dextrose (50 g/l), saline (9 g NaCl/l) and colloids) in the body water compartments. ECF, extracellular fluid; ICF, intracellular fluid.

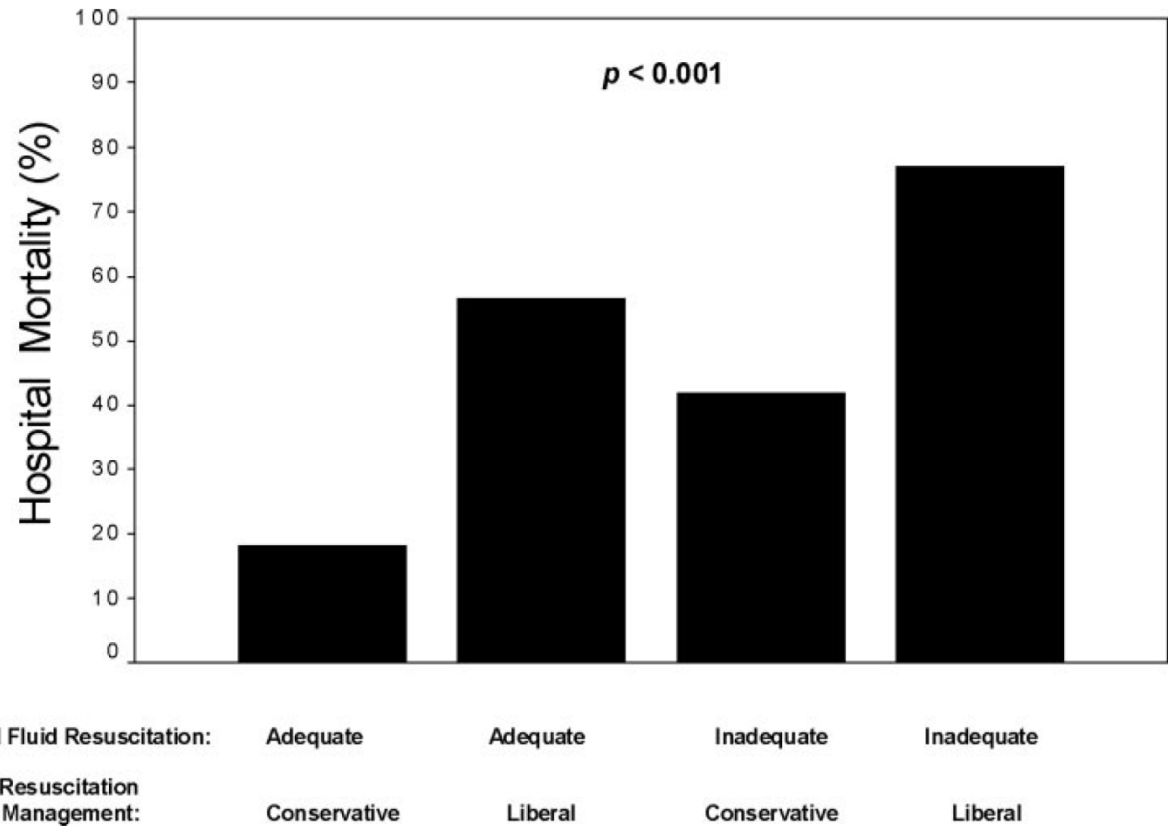
Murphy et al: The Importance of Fluid Management in Acute Lung Injury Secondary to Septic Shock. *CHEST* 2009; 136:102–109

Design: Single Center retrospective analysis of ICU patients

Patients: 212 pts with Acute lung injury (ALI) within 72 hrs of sepsis

Comparisons: Adequate initial fluid resuscitation (AIFR) administration of an initial fluid bolus of > 20 mL/kg prior to and achievement of a central venous pressure of > 8 mm Hg within 6 h after the onset of therapy with vasopressors. Conservative late fluid management (CLFM) was defined as even-to negative fluid balance measured on at least 2 consecutive days during the first 7 days after septic shock onset.

Outcomes: Hospital Mortality

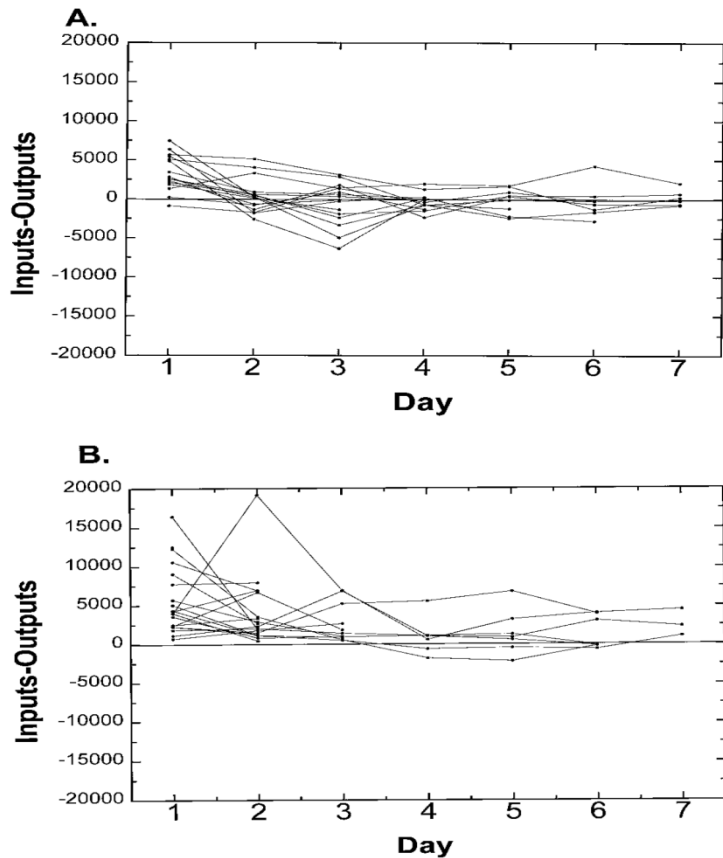


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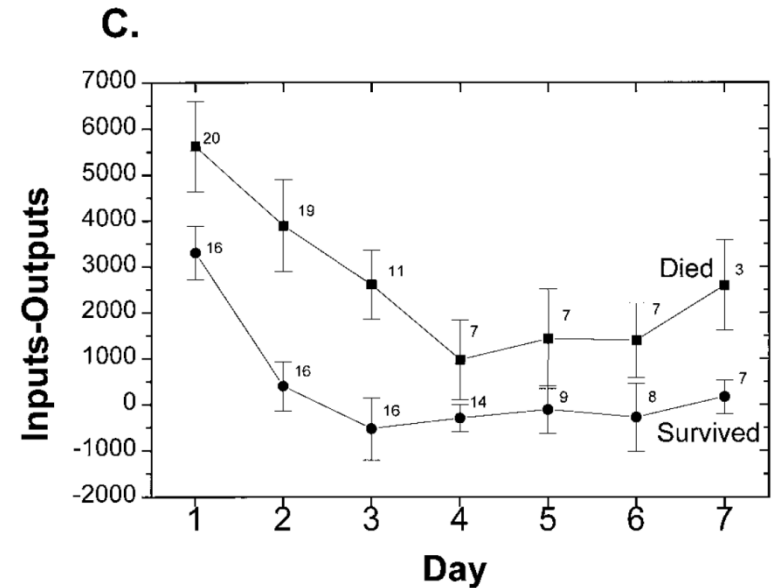
Fluid Accumulation has consequences: It may be missed or unaccounted for

Alsous et al: Negative Fluid Balance Predicts Survival in Patients With Septic Shock* *CHEST 2000; 117:1749–1754*

Daily Fluid Balance



Cumulative Fluid Balance



Fluid balance in subgroups of 36 patients with septic shock. *Top, A: net fluid balance (inputs-outputs) in patients who survived is shown. Middle, B: net fluid balance in patients who died is shown. Bottom, C: the aggregate daily mean (6 SE) values comparing those who survived vs those who died are shown.*

3. Fluid Accumulation has consequences: Underestimation of Severity of AKI

Fluid Accumulation Underestimates Severity of Acute Kidney Injury in Critically-ill Patients

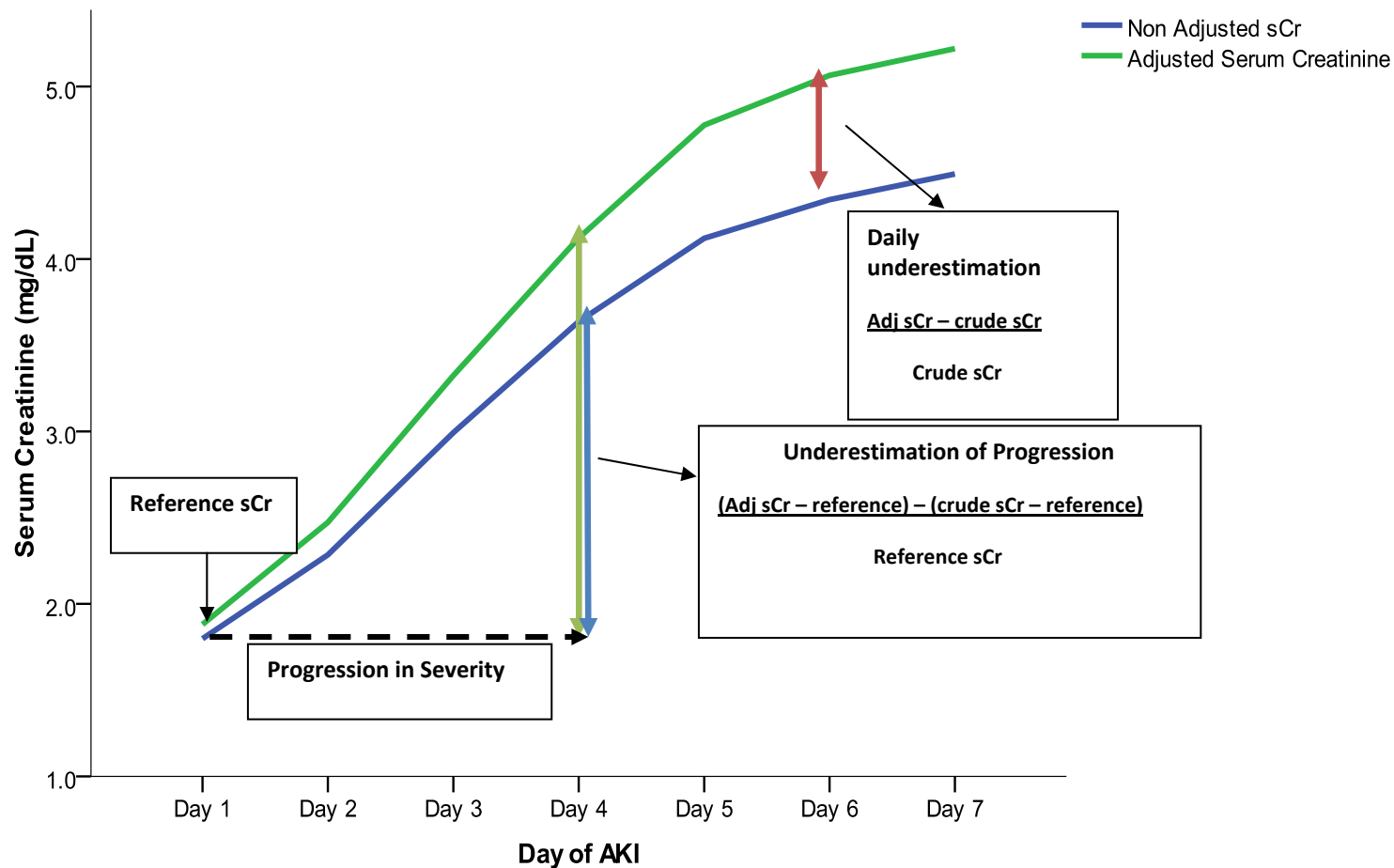
Daily Cumulative Fluid Balance and SCr (adjusted and non-adjusted)

	day 0	day 1	day 2	day 3	day 4	day 5	day 6
cumulative FB - Liters (median)		2.7	3.7	4.95	5.6	6	6.5
IQR 25%-75%		0.50 - 6.20	1.15 - 8.60	1.72 - 10.30	2.50 - 12.00	1.90 - 13.1	1.07 - 11.32
SCr non-adjusted	1.6	2.1	2.8	3.3	3.8	3.85	3.9
IQR 25% - 75%	1.2 - 2.20	1.5 - 2.80	2.1 - 3.75	2.6 - 4.60	2.9 - 5.50	2.9 - 5.55	2.825 - 5.58
SCr - FB adjusted	1.69	2.24	3	3.79	4.29	4.44	4.55
IQR 25% - 75%	1.20 - 2.32	1.61 - 3.06	2.31 - 4.24	2.86 - 5.23	3.23 - 6.29	3.44 - 6.31	3.42 - 6.68



Fluid Accumulation Underestimates Severity of Acute Kidney Injury In Critically-ill Patients

Etienne Macedo, MD¹, Josée Bouchard, MD¹, Sharon Soroko, MS¹, Glenn M. Chertow, MD, MPH², Jonathan Himmelfarb, MD³, T. Alp Ikizler, MD⁴, Emil P. Paganini, MD⁵, Ravindra L Mehta, MD¹. Program to Improve Care in Acute Renal Disease (PICARD) study



Fluid Status impact on Drug Dosing

- Fluid administration is frequently necessary to stabilize ICU patients.
- Fluid overload has however been associated with an increased risk of mortality especially in those with AKI.
- The distribution volume of many drugs has been noted to be increased by 25-50% in critically ill patients esp. those with AKI.
- Fluid accumulation may mask severity of underlying renal injury
- Clinical impact -- one needs to start with higher loading doses and then adjust based on organ function

Schrier RW Clin J Am Soc Nephrol 2010;5:733-9

Koyner JL & Murray PT Bolld Purif 2010;29: 52-68

Roberts JA & Lipman J Crit Care Med 2009;37:840-51



Areas for Consideration

4. Organs responsible for drug handling

Organs

- Kidney
- Liver
- Other Organs

Parameters to Assess Organ Function

- Overall severity of organ failure
- Specific measures of organ function for drug handling
 - Clearance measurements
 - Estimated clearance
 - TDM

Elements of the Scoring Systems

Organ	Variable	SOFA ¹⁰⁸	LODS ¹⁰⁷	MODS ¹⁰⁹
Respiratory	PaO ₂ /FIO ₂	Yes	Yes	Yes
	MV		Yes	Yes
Hematology	Platelets	Yes	Yes	Yes
	WBC			Yes
Liver	Bilirubin	Yes	Yes	Yes
	Prothrombin time			Yes
Cardiovascular	Mean arterial pressure	Yes		
	Systolic blood pressure			Yes
	Heart rate		Yes	
	PAR			Yes
	Dopamine		Yes	
	Dobutamine		Yes	
	Epinephrine		Yes	
	Norepinephrine		Yes	
CNS	Glasgow coma score	Yes	Yes	Yes
Renal	Creatinine	Yes	Yes	Yes
	Blood urea nitrogen			Yes
	Urine output		Yes	Yes

Focus: Renal Function: Augmented as well as Compromised

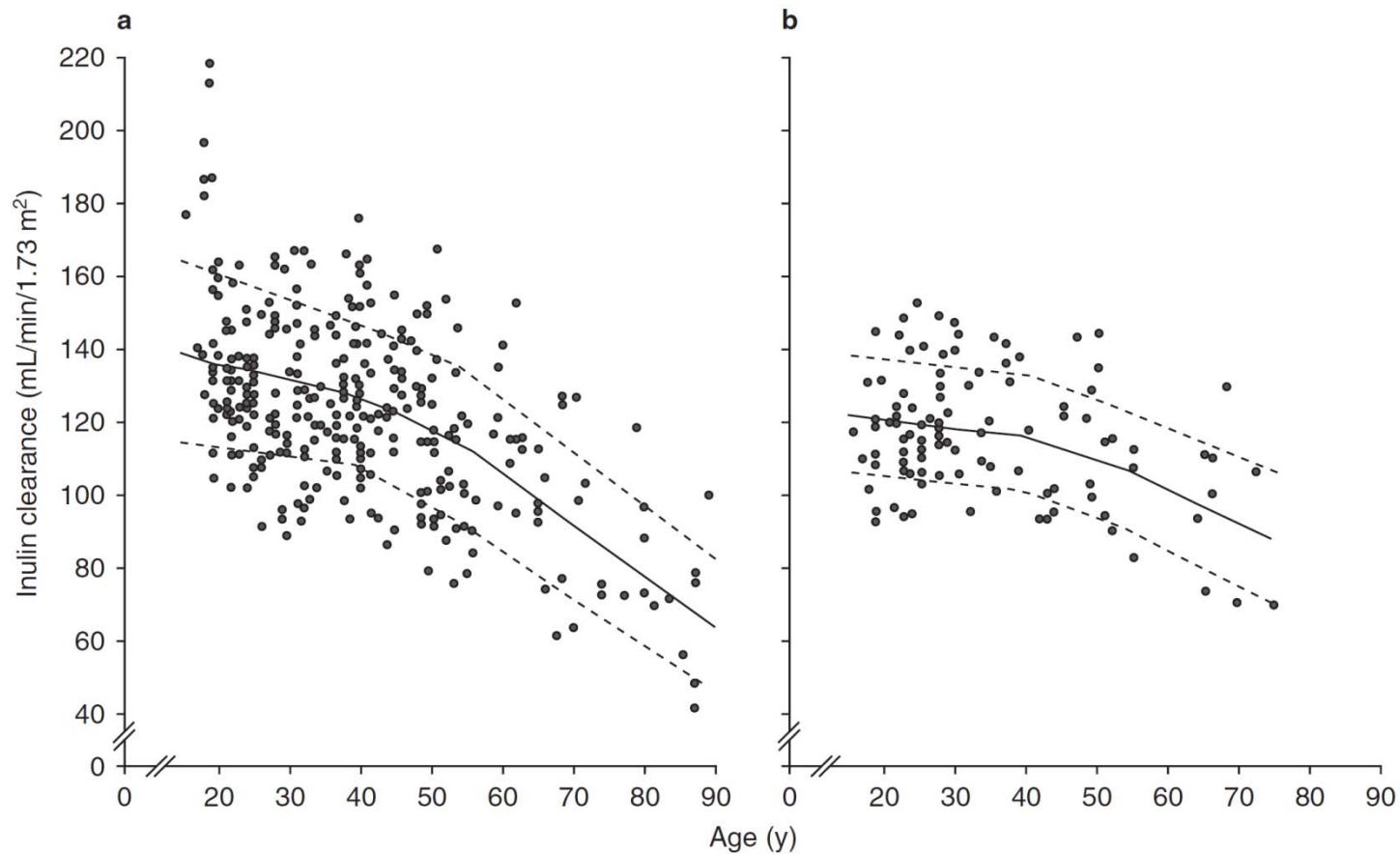
- Changes in renal function are common during course of illness
- Hyperfiltration is often encountered early in the course of MODS and especially in those with burns or trauma and may be as problematic as a decline in renal function.
 - the use of inappropriately low doses of medication can lead to treatment failure and even death
- Hypofiltration may be especially challenging to quantify in those with changing function
- Patients receiving RRT add additional complexity particularly when the therapy is intermittently interrupted.



Udy AA et al Clin Pharmacokinetics 2010;49:1-16

VerbeeckRK Musuamba FT Eur J Clin Pharmacol 2009;65:757-73

Udy AA et al : Augmented Renal Clearance Implications for Antibacterial Dosing in the Critically Ill. Clin Pharmacokinet 2010; 49 (1): 1-16



Normal values of the glomerular filtration rate (GFR) in men and women. Inulin clearance for various ages in mL/min/1.73m² (a) in men and (b) in women. The solid lines represent the mean values of the GFR per decade of age, and the dashed lines represent the values of 1 standard deviation from the mean. (Reproduced from Stevens et al.,[30])

Udy AA et al : Augmented Renal Clearance Implications for Antibacterial Dosing in the Critically Ill. Clin Pharmacokinet 2010; 49 (1): 1-16

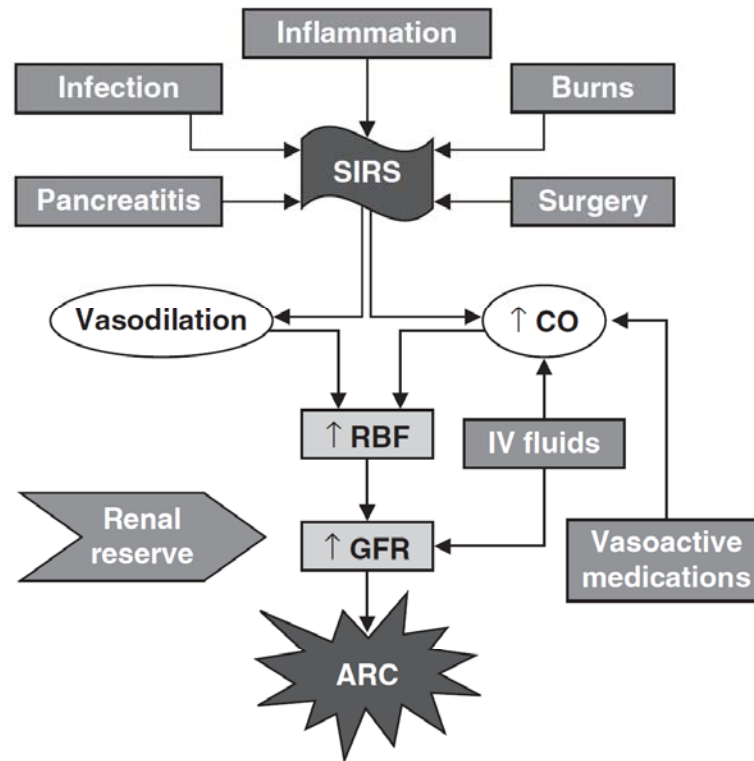


Fig. 2. Mechanisms underlying augmented renal clearance (ARC) in the critically ill. **CO**=cardiac output; **GFR**=glomerular filtration rate; **IV**=intravenous; **RBF**=renal blood flow; **SIRS**=systemic inflammatory response syndrome; ↑ indicates increase.

Martin JH et al Pitfalls of using estimations of glomerular filtration rate in an intensive care population

Intern Med J. 2010 Jan 4. [Epub ahead of print]

Methods: The accuracy of the eGFR (before and after adjustment for actual body surface area (BSA)) was compared with measured and with estimated creatinine clearance using the Cockcroft Gault (CG) formula adjusted for total and lean body weight.

Results: 237 observations were recorded in 47 ICU subjects. These were 1) patients with the primary diagnosis of an isolated head injury (requiring the initiation of osmotherapy or vasopressor infusion for the maintenance of an adequate cerebral perfusion pressure), 2) known or suspected sepsis [27] or 3) subjects with diagnosis of burns. All subjects had normal renal function as defined as serum creatinine concentration <120mol/L at the time of enrolment.

Estimate	Mean difference (95% CI) for all observations	Mean difference (95% CI) for 1st observation
eGFR (ml/min/1.73)	-12 (-20 to -3), p=0.33	-25 (-4 to -47) p=0.06
eGFR undadjusted (ml/min)	5 (-2-13), p=0.32	-8 (-29-13), p=0.17
CG (ml/min)	17 (9 to 24), p=0.48	2 (-17-22), p=0.3
CG using IBW (ml/min)	12 (4-21), p=0.34	-7 (-28-15), p=0.11

positive value = under prediction, negative value = over prediction

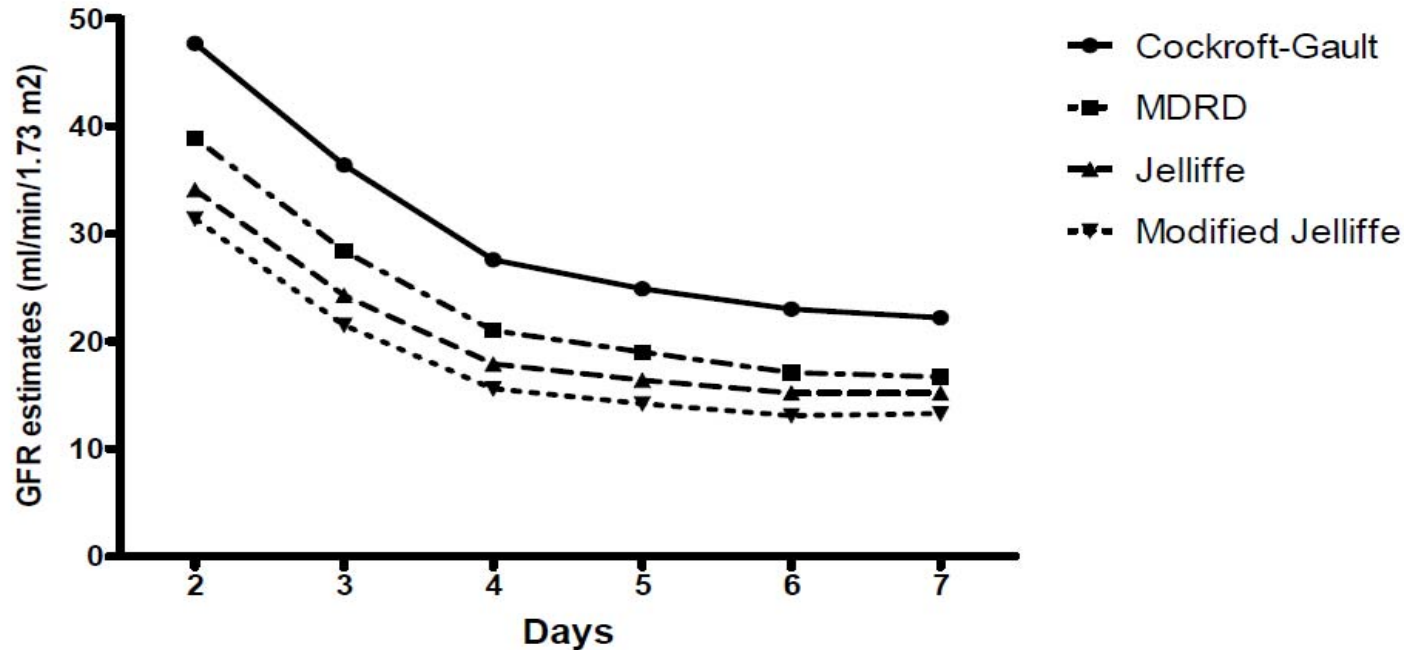
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Bouchard et al: Comparisons of different techniques for estimating glomerular filtration rate in critically ill patients with acute kidney injury

Nephrol Dial Transplant. 2010 Jan;25(1):102-7

GFR estimates by Cockcroft-Gault, MDRD, Jelliffe and Modified Jelliffe



Jelliffe: $((\text{Volume of distribution} \times (\text{sCr on day1} - \text{sCr on day2})) + \text{creatinine production}) \times 100/1440/\text{average sCr}$.

Modified Jelliffe: Since this equation takes into account sCr fluctuations and creatinine production over time, but not fluid balance variations, which can also significantly influence serum creatinine measurements [15], we adjusted every sCr according to the cumulative daily fluid balance using the following equation [15]: **Adjusted creatinine = sCr × correction factor** **Correction factor = [hospital admission weight (kg) × 0.6 + (daily fluid balance)]/hospital admission weight × 0.6.**

Areas for Consideration

5. Drug Disposition

- Drug Absorption
- Drug Distribution
 - Pharmacokinetics
 - Pharmacodynamics
- Drug Metabolism
- Drug Transport
- In-Silico modeling
 - Drug Drug interactions

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Drug Distribution

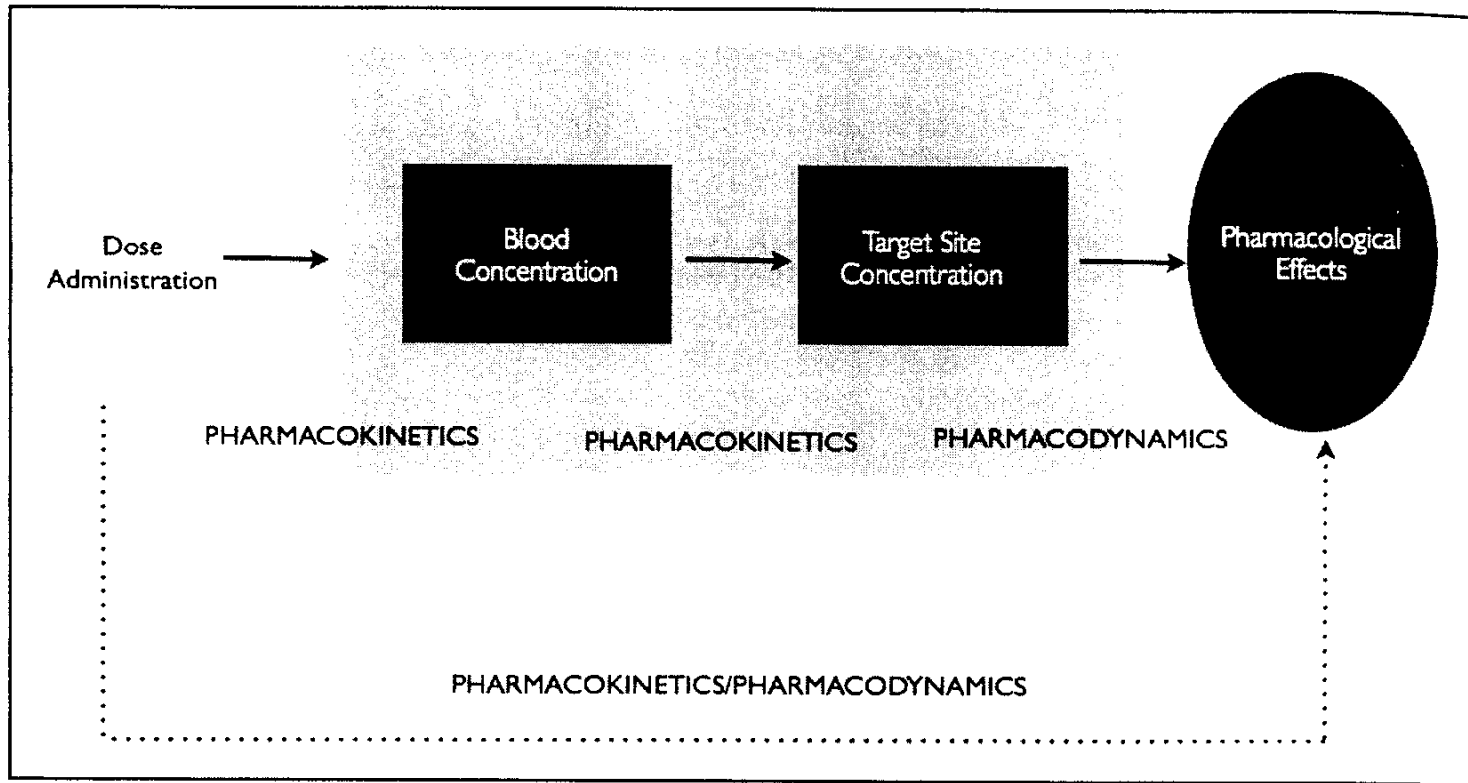


Fig. 1. Interrelationship between pharmacokinetics and pharmacodynamics and link between the two concepts by pharmacokinetics/pharmacodynamics

Drug Distribution

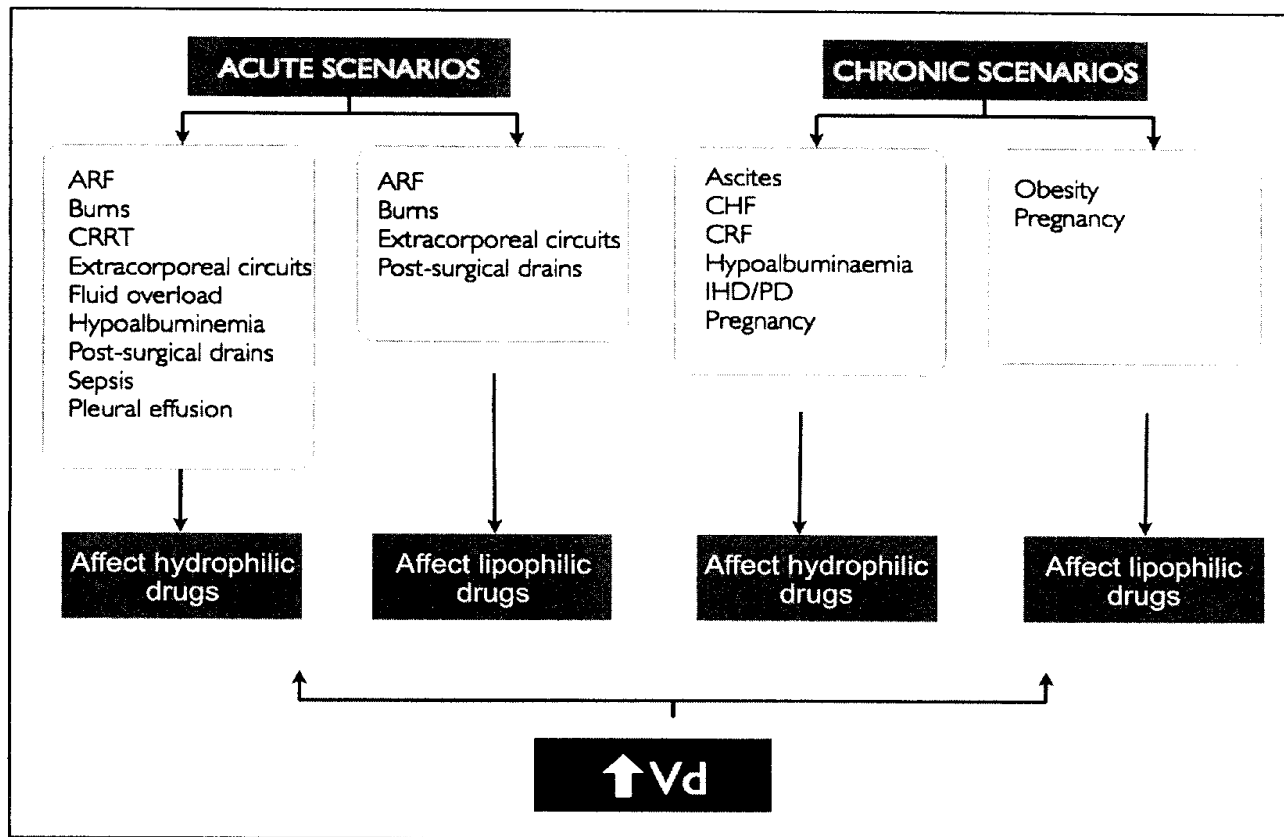


Fig. 3. Classification of the increases in volume of distribution as acute or chronic, and drugs likely to be affected by each situation due to their physicochemical characteristics. AKI: Acute kidney injury; CRRT: Continuous renal replacement therapy; CHF: Congestive heart failure; CKD: Chronic kidney disease; IHD: Intermittent hemodialysis; PD: Peritoneal dialysis

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Drug Distribution

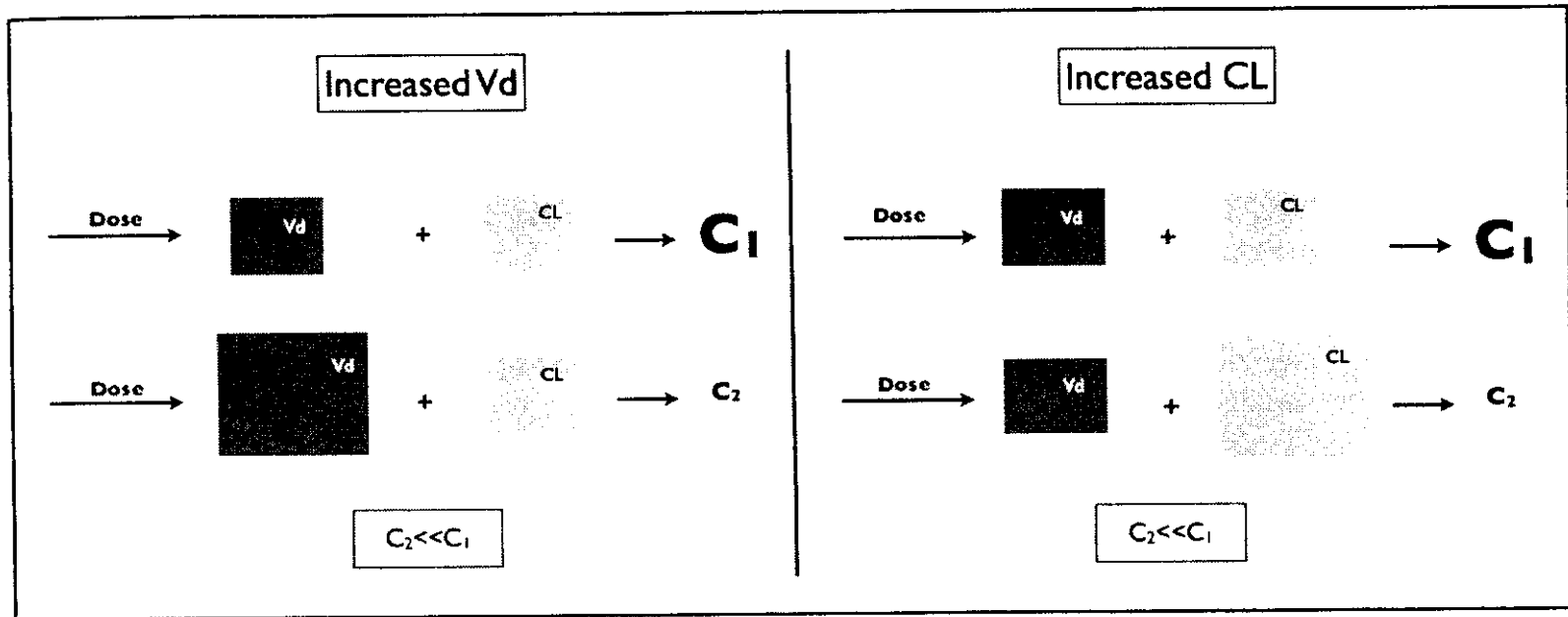


Fig. 2. Changes in drug concentrations due to increased clearance (CL) and volume of distribution (Vd). In the left panel, the lower schematic shows that increased volume of distribution leads to decreased serum concentration (C_2) compared with that observed with a smaller volume of distribution (C_1). In the right panel, increased clearance causes a lower serum concentration (C_2) compared with that resulting from the lesser clearance denoted by C_1 .

What is suspected regarding Drug Disposition in MODS?

- Erratic gastrointestinal absorption due to gut hypoperfusion, gut barrier injury, or postoperative ileus;
- Variations in the extracellular fluid volume as a response to trauma, the resuscitation fluid load and/or as a consequence of continuous renal replacement therapy;
- Altered drug metabolism due to the systemic inflammatory response or liver and or kidney dysfunction as a component of MODS.
- Drug-drug pharmacokinetic and or pharmacodynamic interactions as the result of polypharmacy

Heintz BH et al *Pharmacother* 2009;29(562–577)

Pea F, et al. *Clin Pharmacokinet* 2008; 47 (7): 449-462



AKI associated with Decreased Drug Metabolism

- Critically ill patients with early onset AKI have a higher residual non-renal clearance of some drugs than patients with CKD who have a similar creatinine clearance.
 - This may be the result of less exposure to or accumulation of uremic waste-products that may alter hepatic, gut, or intra kidney metabolism.
- Drug administration early in this clinical situation based on data from CKD patients would result in the attainment of lower than desired and possibly sub-therapeutic serum concentrations.



Vilay AM, Churchwell MD, Mueller BA. Crit Care 2008;12:235
Nolin, TD. Curr Opin Nephrol Hypertension 2008;17; 255-559

Drug Transporters in the Kidney

Feng, LaPerle, Chang & Varma

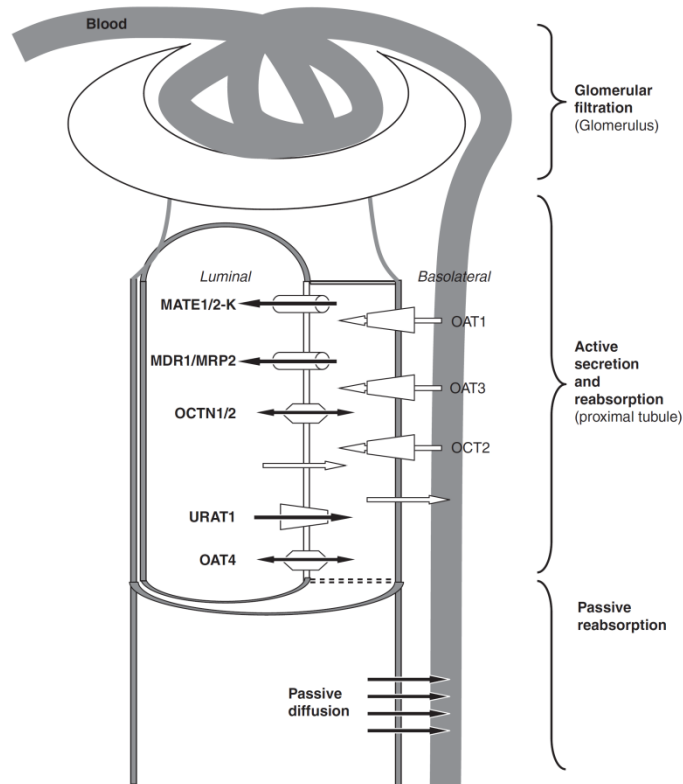


Table 1. The reported drugs as substrates and inhibitors of major renal uptake transporters.

Transporter (gene)	Substrates	Inhibitors
OAT1 (SLC22A6)	Cidofovir, acyclovir, methotrxate, adefovir, pravastatin	Probenecid, adefovir, naproxen, indomethacin, cephaloridine, furosemide
OAT3 (SLC22A8)	Ranitidine, methotrexate, cidofovir, cimetidine, famotidine, sitagliptin, pravastatin, valacyclovir, ochratoxin A	Probenecid, quinidine, indomethacin, furosemide, bumetanide, cimetidine, pravastatin, cefataxime, cefamandole, cephaloridine
OCT2 (SLC22A2)	Procainamide, cimetidine, metformin, varenicline, triamterene, pinodol, amiloride	Quinidine, cimetidine, trimethoprim, ranitidine

OAT: Organic anion transporter; OCT: Organic cation transporter.

Figure 1. Schematic of nephron, indicating the sites and mechanisms involved in the glomerular filtration, secretion and reabsorption process, which determine the renal clearance. Major transporters known to be localized in the proximal tubule were also depicted.

Feng et al: Renal clearance in drug discovery and development: molecular descriptors, drug transporters and disease state Expert Opin. Drug Metab. Toxicol. [Early Online] 2010



Areas for Consideration

6. Quantification of Function

- Renal
- Liver
- Contribution of individual organs in setting of different levels of organ failure



21st Century Tools for Organ Function Quantification

- New approaches to measure and estimate glomerular filtration rate
 - Cystatin C and Beta trace protein
 - MDRD eGFR, CKD-EPI, others
- Comprehensive evaluations of kidney elimination pathways
- Pharmacogenetic and Phenotypic measures of metabolic activity



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Quantification of Renal Function

- Filtration does not provide an accurate measure of the contribution of kidney to renal excretion of all drugs. Especially...
 - Those that are extensively secreted, and
 - Those that are metabolized in the kidney or other organs
- New quantitative techniques have been developed and validated but rarely has one of these approaches been used in MODS patients.



Clinical Application of Assessing Alterations in Renal Elimination Pathways

- Dowling et al developed and validated a cocktail approach to characterize the influence of disease and on tubular secretion as well as GFR and the degree of renal reserve .
 - Iothalamate to measure GFR,
 - PAH to measure RPF & anionic secretion, and
 - Famotidine to measure cationic secretion
- Gross et al developed a similar approach and the cocktail they devised consisted of:
 - Sinistrin to measure GFR,
 - PAH to measure RPF & anionic secretion,
 - Pindolol to measure cationic secretion
 - Fluconazole as an index of passive reabsorption



Dowling TC, et al *Kidney Int* 2001;59:295-303

Gross AS, et al *Br J Clin Pharmacol* 2001;51:547-55

Tett SE et al *Clin Pharmacokinet* 2003; 42 (14): 1193-1211

Quantification of Liver Function

- Liver dysfunction during critical illness is associated with a poor outcome that is independent of other organ dysfunctions; critical risk factors include;
 - shock, sepsis, mechanical ventilation with positive end-expiratory pressure, and major surgery.
- Diagnosis of hepatic dysfunction in its early stages may be difficult due to insensitivity of standard liver function tests and disease severity scoring criteria.
- Most organ failure scoring systems grade the severity of hepatic dysfunction based on serum bilirubin and/or transaminases.



Verbeeck RK Eur J Clin Pharmacol (2008) 64:1147–1161

The “Cocktail” Approach for Phenotyping Drug Metabolizing Enzymes and Transporters

- Numerous drug cocktails have been published. The earlier cocktails often used less selective marker drugs because the molecular identity of the respective enzymes or transporters was unclear.
- In all cocktails, the selection of metrics is determined by several factors, including the specific objective of the respective study, the availability of analytical methods, and the balance between expense and validation.

Even recent phenotyping cocktails often contain substances or use phenotyping metrics that are not optimal for use in ICU patients.



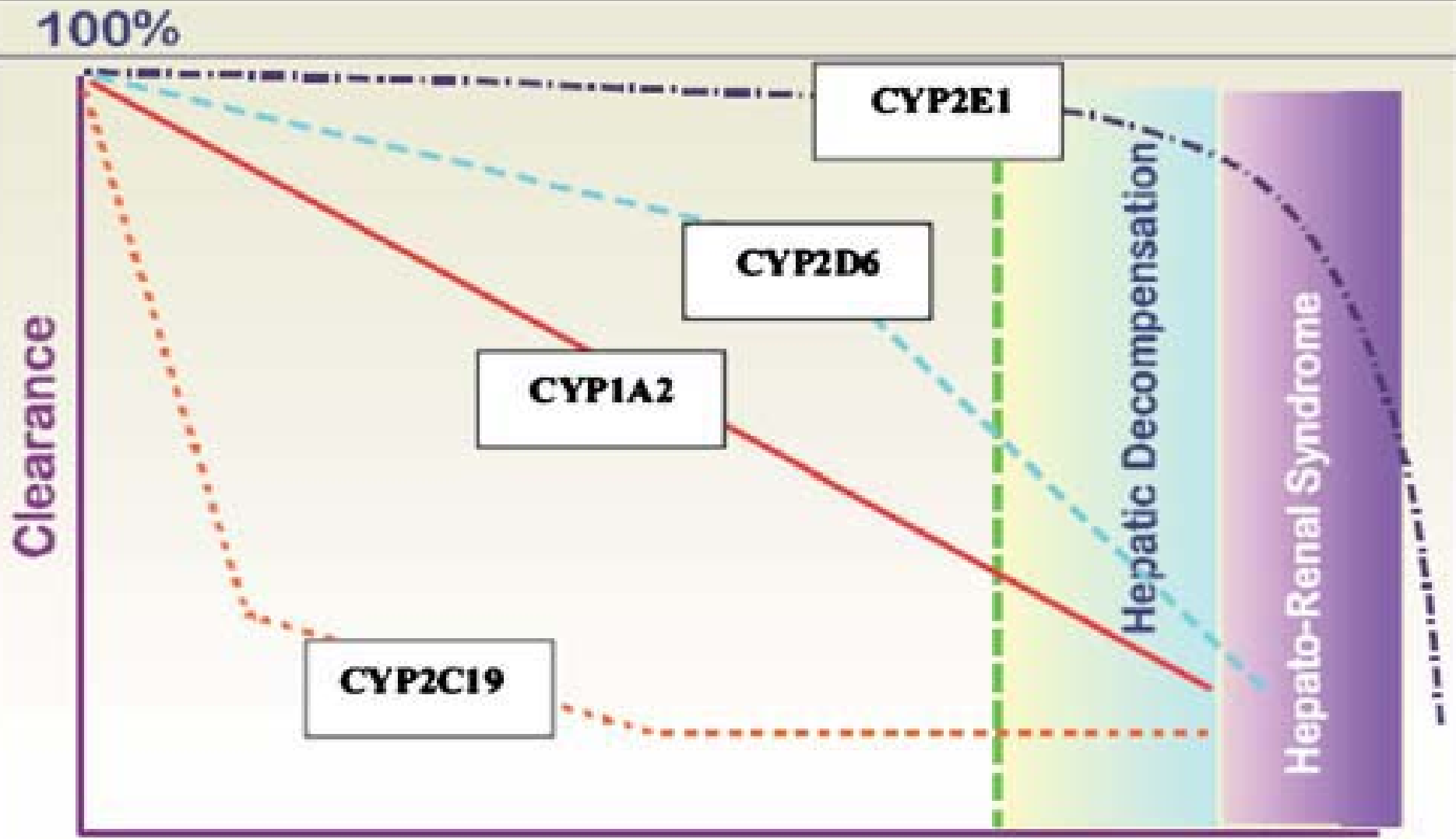
Fuhr U, et al Clin Pharmacol Ther 2007;81:270-83

Drug Metabolism in Liver Disease

- Frye and colleagues evaluated 20 patients with different etiologies and severity of liver disease. [Eleven had Child-Pugh scores of 5-6 & 9 had scores of 7-11] The 20 age-, sex-, and weight-matched healthy volunteers as well as the patients all had normal renal function, CLcr > 90 mL/min..
- All participants received a cocktail of 4 oral drugs simultaneously, caffeine, mephenytoin, debrisoquin, and chlorzoxazone, as in vivo probes of the drug metabolizing enzymes CYP1A2, CYP2C19, CYP2D6, and CYP2E1, respectively.
- They found that CYP enzyme activity was differentially affected by the presence of liver disease. CYP 2C19 activity was the most profoundly affected. Progressive disease was associated with significant declines in the function of all CYPs.



Frye RF, et al Clin Pharmacol Ther 2006;80:235-45



Quantification of Renal Function in those with Liver Disease

- Renal function should be routinely monitored in all patients with advanced cirrhosis, especially those with ascites
- Serum creatinine measurement is still the most useful and widely accepted method for estimating renal function in patients
- Estimation of eGFR or CLcr is not recommended.



Ginas P and Schrier RW. N Engl J Med 2009;361:1279-90.

What is known regarding Drug Dosing in MODS?

- In critically ill patients, several drugs may need dosing regimens significantly different from those suggested in clinically stable patients.
- CAUTION should be applied when using nephrotoxic or hepatotoxic drugs, with a special emphasis on:
 - timely drug dosages,
 - changes in renal and metabolic clearance,
 - fluid volume status, and
 - drug interactions.



Knowledge Gaps I

- How does one assess the contribution of the kidney dysfunction in comparison to the dysfunction of other organs, such as the liver, gut, and heart, on drug disposition in patients with MODS?
- What index of renal, liver, or other organ function should one use as a guide for drug dosage regimen individualization / adjustment in patients with MODS?
 - This will require an assessment in Adults, Pediatrics, Geriatrics, and those with other co-morbid conditions such as, Inflammatory conditions, Obesity, Burns, and Trauma



Knowledge Gaps II

- How does one individualize drug dosage regimens and evaluate its appropriateness when organ function is changing rapidly?
- What is the role of systemic illnesses such as cancer, diabetes, sepsis, etc and the therapies used to manage them on drug disposition or dynamics in MODS?
- Do pre-clinical models of MODS or co-morbid chronic diseases predict the human condition?
- What is the role of “in silico” modeling ?



Knowledge Gaps III

- Is therapeutic drug monitoring and PK modeling an effective means to optimize drug therapy outcomes?
- How can one characterize the influence of more than one acute or chronic disease / condition on the disposition of a drug?
- How can this information be used to design drug dosing recommendations in patients with MODS?





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Methodology

Identification of What is Known

- Medline database from January 2000 through March 2010 for literature with the medical subject headings: 'acute renal failure', 'acute kidney injury', 'chronic kidney disease', 'MODS', 'MSOF', 'hepatorenal syndrome', 'liver failure', 'cirrhosis', 'heart failure', 'intensive care' and 'critically ill'. All searches were limited to studies of human subjects and were conducted as advanced searches cross-referenced with 'pharmacokinetics' as well as 'drug dosing'.
- The searches produced a total of 6,456 citations.
- Each search was reviewed by a panel of experts to ascertain its relevance to one of the three focuses of the group.



Clinical Presentation

- The clinical presentation of MSOF / MODS has evolved over the last 30 years.
- Although most cases of MODS occur secondary to shock, sepsis, and severe trauma a multiplicity of other risk factors have been identified.
- Initially post injury MSOF / MODS was thought to be an overwhelming, uncontrolled sepsis response.
- Over 90% of patients who develop MSOF / MODS have early respiratory dysfunction. Cardiac dysfunction often is observed within the next day, followed by hepatic dysfunction within 4-6 days and renal dysfunction in 5-7 days.

Mizock BA Dis Mon 2009;55:476-526

Dewar D et al Injury, Int. J. Care Injured 40 (2009) 912–918



What is the Influence of Care Factors on Drug Disposition in MODS?

- Fluid overload
- Tissue perfusion
 - pressors,
 - vasodilators and inotropes
- Mechanical Ventilation
- RRT
- Other support modalities e.g. ECMO



Challenges in Patient Care

- The heterogeneous patient population and lack of agreement on a single standardized scoring system limit the tracking of progress in the management of MODS.
- The incidence and the magnitude of MODS has decreased over the last 20 years, but it still remains a significant issue.
- The recent European “Sepsis Occurrence in Acutely Ill Patients study” of 3,147 ICU admissions revealed that 71% of ICU patients had significant organ dysfunction and that sepsis was present in 41% of those with MODS
- Thus there remains a great need to improve our diagnostic and therapeutic approaches if we hope to be able to improve patient outcomes.



Vincent JL Crit Care Med 2006;34:344-53

Fluid Accumulation is associated with adverse outcomes

Summary of clinical studies showing an association between fluid balance and clinical outcome

Study, ref.	Year	Number of patients	Design	Population	Intervention	Outcome
Simmons [50]	1987	113	P, C	ARDS	N/A	mortality associated with positive daily/cumulative fluid balance and weight gain
Schuller [45]	1991	89	R, C	ALI/ARDS	N/A	mortality associated with higher positive fluid balance >1 l over 36 h (50 vs. 26%, p < 0.05) along with longer duration of MV and ICU/hospital stay
Goldstein [48]	2001	21	R, C	pediatric AKI	N/A	mortality associated with higher %FO at RRT initiation (34 vs. 16.4%, p = 0.03)
Brandstrup [52]	2003	172	RCT	elective colorectal surgery	restrictive vs. standard peri-operative fluid strategy	restrictive strategy reduced post-operative weight gain and complications (33 vs. 51%, p = 0.003)
Foland [46]	2004	113	R, C	pediatric AKI	N/A	mortality associated with higher %FO at RRT initiation (15.5 vs. 9.2%, p = 0.01)
Gillespie [47]	2004	77	R,C	pediatric AKI	N/A	mortality associated with higher %FO at RRT initiation (>10%, RR 3.02, p = 0.002)
Goldstein [49]	2005	116	R, C	pediatric AKI	N/A	mortality associated with higher %FO at RRT initiation (25.4 vs. 14.2%, p = 0.03)
Sakr [14]	2005	393	P, C	ALI/ARDS	N/A	mortality associated with positive cumulative fluid balance (+4.4 vs. -3.0 l, OR 1.5, p = 0.003)
Uchino [51]	2006	331	P, NR	critically ill	N/A	mortality associated with positive fluid balance (OR 1.0002 per each ml/day, p < 0.01)
Wiedemann [15]	2006	1,000	RCT	ALI/ARDS	conservative vs. liberal fluid strategy	conservative strategy had lower cumulative 7-day fluid balance (0.13 vs. 6.9 l, <0.001), improved gas exchange, shorter time on ventilator and ICU stay, no difference in rate of RRT or mortality

P = Prospective; R = retrospective; C = cohort; RCT = randomized clinical trial; NR = nonrandomized; ALI = acute lung injury; ARDS = acute respiratory distress syndrome; N/A = not applicable; %FO = percentage fluid overload; RR = risk ratio; MV = mechanical ventilation.

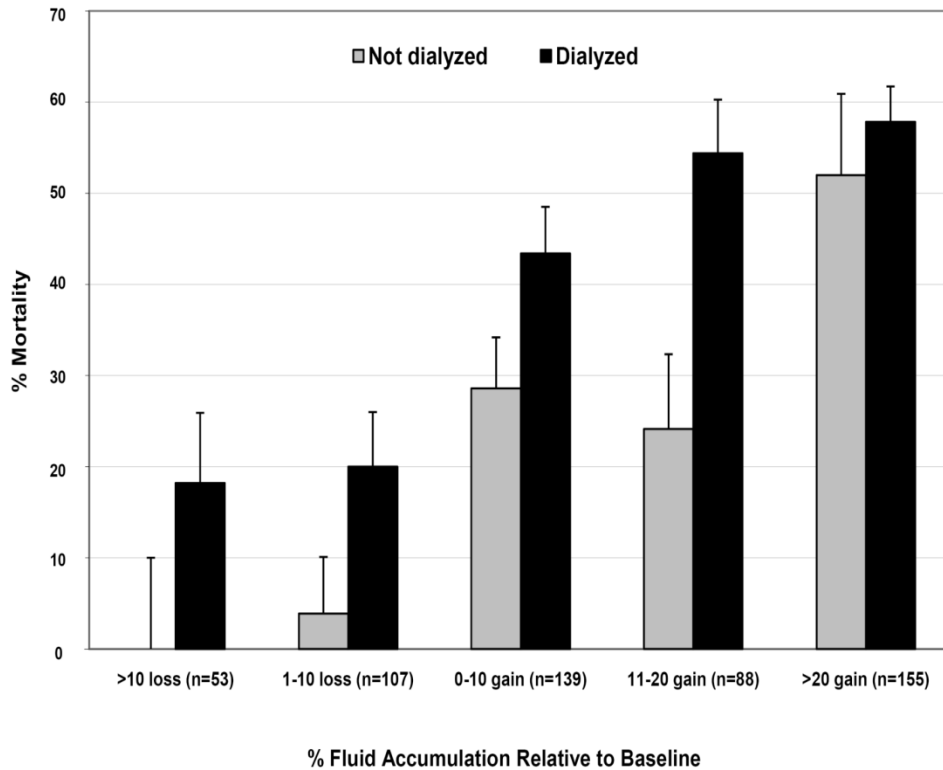
Kidney Disease: Improving Global Outcomes



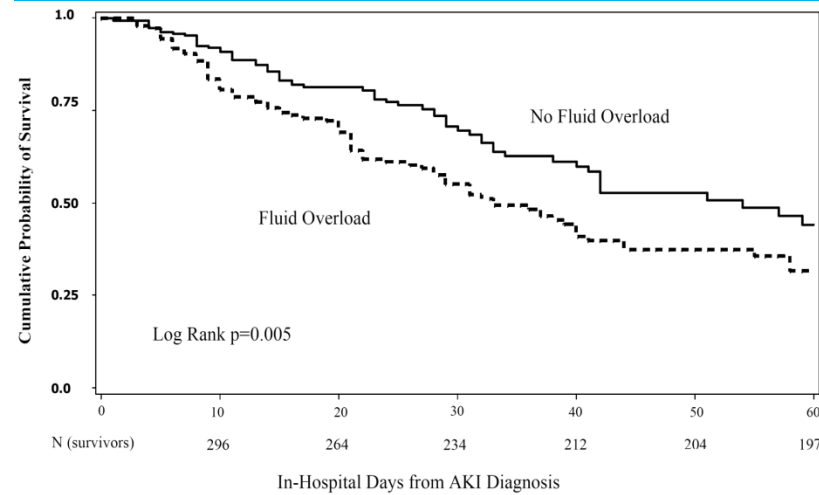
Fluid Accumulation is associated with adverse outcomes

Effect of Fluid Overload in Critically Ill Patients with AKI

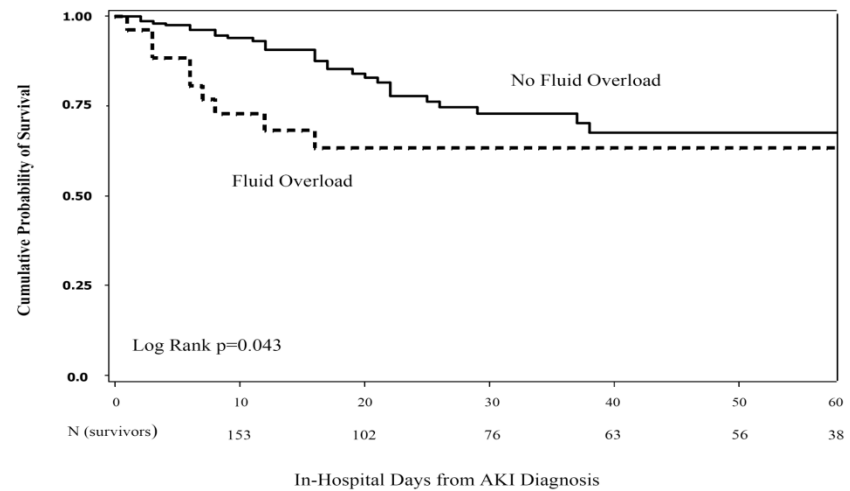
PICARD Study (618 critically ill patients with AKI, 396 required dialysis)



Dialyzed Patients



Non-Dialyzed Patients



Adjusted OR for death with %FO >10% at dialysis initiation: 2.07 (95% CI 1.27-3.37)
Adjusted OR for death with %FO >10% at dialysis cessation: 2.52 (95% CI 1.55-4.08)



Fluid Balance and AKI

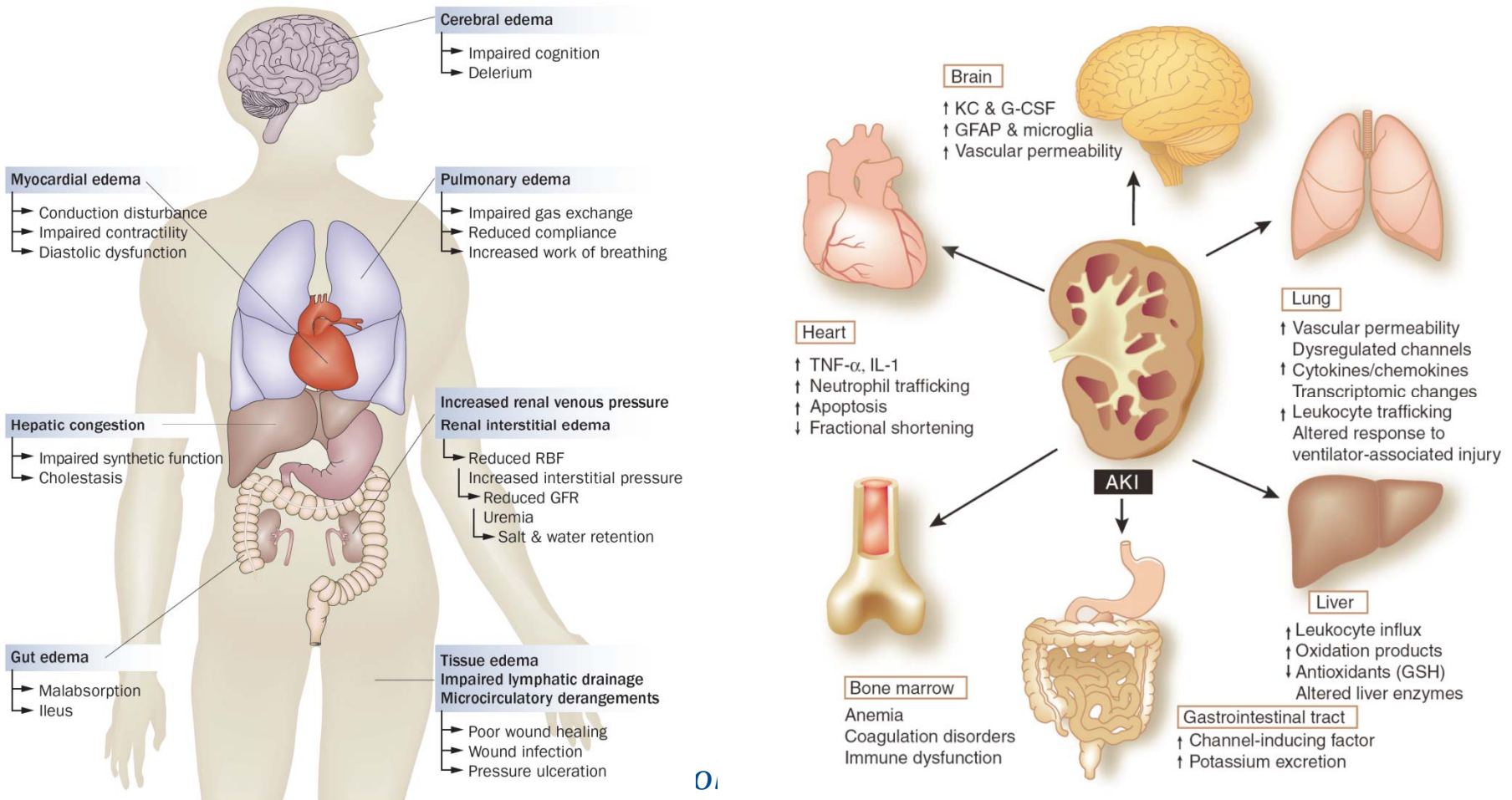


Figure 2 | Pathological sequelae of fluid overload in organ systems. Abbreviations: GFR, glomerular filtration rate; RBF, renal blood flow.

Prowle, J. R. et al. *Nat. Rev. Nephrol.* 6, 107–115 (2010);