so for the final part of this

pharmacokinetics and acute kidney injury

the overview is shown here

and very similar in topics to what weve

already covered for chronic kidney

disease

as weve mentioned drugs are commonly

prescribed and particularly in patients

with acute kidney injury theyre

generally admitted to hospital and

theyre acutely unwell

so we need to think about how our dosing

regimen may differ to that for patients

with normal kidney function

so aki is a much more complicated

scenario for ckd thats because aki

varies in severity duration and also its

treatment

we get changes over a much shorter time

frame

than we would in chronic kidney disease

and its already mentioned its often

observed in the context of critical

illness so were getting multiple other

physiological impacts

so changes in kinetics seen in patients

with acute kidney injury may actually

reflect more about changes in critical

illness or changes related to

sepsis rather than aki on its own so

theres multiple factors

which are impacting on measurements of

pharmacokinetics in these patients

aki has illdefined impacts on

biochemistry and clearance and this

includes a clearance of drugs

electrolytes and also uremic toxins ive

already shown you that uremic toxins can

impair

nonrenal clearance

well with the aki it might mean that

theyre increasing or decreasing at

rates which we dont understand

maybe that doesnt even change to a

significant extent were just not sure

theres not enough data

so the net effect

of this

these various issues is that theres

marked variability in drug

concentrations and patient response

and therefore if you look at drug dosing

guidelines they tend to be

very vague

or even absent

because its too hard to comment on them

but we need to think about this as

youre aware there is an epidemic of

acute kidney injury this is the way it

feels at least to me as a nephrologist

seems to affect more than 0 to 0

percent of patients admitted to hospital

worldwide

many of these cases of aki are very low

grade and they resolve rapidly

but patients with more significant aki

particularly if you go to intensive care

the mortality may approach

ive already mentioned that sepsis is a

major cause and since antibiotics are

used for the treatment of sepsis

then its crucial that we obtain

appropriate concentrations of those

antibiotics to ensure that were

maximizing clinical outcomes

many of these patients who come in with

acute kidney injury have complex

comorbidities

and theyre taking multiple drugs and so

this increases the overall risk of

management in acute kidney injury and so

we need to disadjust these

medicines

as you probably know in many cases when

someone comes in with acute kidney

injury we find ourselves stopping a lot

of medicine so that can make some

decision making easier

but there are a number of medicines we

dont stop and theres medicines we

start so we need to have an approach to

dosing

um

and patients who have acute kidney

injury and critically unwell may receive

arena or replacement therapy such as

dialysis

which may also impact on clearance

and pharmacokinetics but i wont be

talking about that today because thats

the topic of another presentation

so how do we diagnose acute kidney

injury

well again its based on serum

creatinine

and the way we stage acute kidney injury

is based on how high the creatinine

rises relative to the baseline

so here stage one is when its up to two

times uh the baseline or if it raises by

more than zero point three milligrams

per deciliter or micromoles per

liter

if it goes up to nearly three times at

stage two and if its more than three

times its stage three

or if the person has a serum creatinine

concentration that increases by more

than four

and theres also other markers which

relate to urine output

so this tells us about the stage or

severity of acute injury note that this

is not telling us what the actual kidney

function is it is not telling us the gfr

why is that

well since what we were talking about

before

um

we we can only use creatinine to

interpret kidney function when were at

steady state and aki is a is a dynamic

condition

if we look at a scenario here these are

some simulations based which are

published in 9 which there are a few

assumptions made but even still i think

its uh is a very useful

representation of what happens in real

life

if you have an acute event that all of a

sudden drops your gfr to

it takes a few days until you get to a

new steady state

if your gfr drops down to

it takes much longer and thats because

the halflife of creatinine becomes so

much longer than the time to steady

state is much longer

so what were seeing here is that your

creatinine concentration is changing

constantly over days

youll often see written in the notes

certainly where i live

where people write down evolving aki

progressively deteriorating kidney

function

not true

obviously it depends on the scenario

were seeing the creatinine going up not

because the kidney function is getting

worse but because we still havent got

to a new steady state

so that means that in the onset of acute

kidney injury whatever the creatinine

concentration that we see

that underestimates the actual kidney

function if we were to put that number

into for example cockroft

or

or a ckd epi formula

and therefore those formulas dont apply

if we compare them to the recovery phase

what we can see here is that as the

kidney functions improving

youll get

we need to wait for give time for the

kidney function to come down for the

to come down so any measures of

creatinine during a recovery phase

understate how good the kidney function

is meaning the kidney function is better

than you would estimate from the

creatinine during the recovery phase

so this demonstrates why we shouldnt be

using egfr to measure gfr to estimate

the

kidney function for the purposes of drug

dosing in patients with acute injury

there have been some more complex

formulas that have been developed which

look at the rate of change between

two creatinine measurements which can

then be used to predict kidney function

or gfr at that time point

but theyre not routinely used because

of their complexity

and weve got an acutely dynamic

situation

this has led to uh exploration into

alternative biomarkers of acute kidney

injury and you can see here for example

in this older paper now

cystatin c is mentioned there ive also

ive so ive used this clinically and

ive done research using cystatin c

similarly ive done it using endgal as

well some of you might have also been

involved with studies looking at these

other tests

these tests these other biomarkers show

damage at an earlier stage and help to

quantify gfr

compared to these later stage

measurements that we use such as serum

creatinine

so whats the impact of acute kidney

injury on pharmacokinetics well this is

a short presentation because essentially

we dont have much information

what happens with absorption metabolism

theres extremely limited data as it

happens we dont give oral tablets or

capsules or formulations to many

patients with

severe acute kidney injury but sometimes

we do

and so theres very limited data and the

data that we have is confounded by the

critical illness which frequently has

its own impacts

what about volume distribution well

again this is quite variable

often it will increase an acute kidney

injury but this is largely because the

studies where this has been measured

have been critically all patients with

sepsis and acute kidney injury in these

cases the antibiotic

antibiotic flame distribution has been

shown to vary tenfold or even more so it

can be quite significant

and this can be impact on by multiple

factors for example we give lots of iv

fluids

during resuscitation

these can all increase on distribution

vasoplegia and capillary leak can cause

edema and pleural effusions or ascites

which further increases the volume of

distribution and they can be changed in

protein binding

similar to the discussion that we had

with chronic kidney disease

this as you can see is all largely

changes in water

not in

for example adipose tissue and therefore

changes in volume distribution are more

likely to occur in antibiotics or other

drugs that are hydrophilic

this is some real data in patients

who are critically ill with acute kidney

injury who required continuous renal

replacement therapy

using the drug meropenem

what we can see here is that despite

separation of two different doses 00

milligrams and 000 there is no clear

separation in the concentration time

profile so each concentration time

profile here affects a different patient

and we can see here that some patients

have extremely high concentrations and

some patients have extremely low

concentrations and very different rates

of elimination based on the halflife so

it really shows a lot of heterogeneity

between

these patients within the population

this then impacts on for example with

meripenem differences in the trough

concentration

and thats important because the

meripenem being

a bit lactamlike drug

the carbopenem

its main determinant of efficacy is a

time above mic

and therefore this would suggest that

were overdosing some patients

tons of bacteria purposely on the same

vancomycin there was a lower target seen

in some patients

this is showing the impact of sepsis on

on antibody concentrations so we can see

here if we compare volunteers with those

with sepsis

who received pipricillin

and this is looking at this is the

plasma concentration here so we can see

here the patients with sepsis given the

same dose of pipracillin compared to

volunteers have a much lower

concentration

and a longer elimination halflife than

we see with volunteers

so this is important because it probably

reflects an expanded volume of

distribution

but we dont know if theres also impact

of uh clearance here as well

the

um and so is this important well it

depends on what the mic is being

priscilla and its time above mic thats

most important

and whether or not these concentrations

are above the mic or not

the same matters that also apply when

were looking at muscle and subcutaneous

tissue

concentrations where

there are marked differences between the

patients who are volunteers and those

who

have sepsis

where generally the concentrations are

lower in those with sepsis

and this is probably a volume of

distribution issue but all of these

patients also had acute kidney injury

theres very few studies looking at

patients

in patients with acute kidney injury

i myself have tried to do it and its

very difficult to recruit patients

because when theyre presenting to

hospital theyre acutely unwell its

its very hard for them to consider

consent related issues

but the few studies that have been

performed

theyre all in critically ill patients

and therefore theres other factors that

are

present

it appears a change in kinetics that

there is not a nephron drop out

so

considerations around the intact nephron

hypothesis that we discussed with ckd

may not apply an acute kidney injury

this is because the relationship between

filtration active secretion metabolism

just is still too poorly defined

an interesting study looked at what

happened with patients who had a

unilateral nephrectomy

so this is a useful marker or

model for acute kidney injury because

with that when you have when you when

you surgically removed a single kidney

its similar to a decrease in your gfr

by fifty percent all of a sudden

so they compared what happened with the

tenderloin amicason

and so one month post operation

clearance was reduced in both the tunnel

and amicaison and as you know both of

these

drugs are um have a high proportions

freely eliminated

but in months afterwards clearance

had almost normalized for atenolol but

not amy casen so i suggested theres

been some sort of compensatory process

during that time

we know that when you do remove one

kidney then there is an increase in um

in filtration and the other in the

opposite kidney thats what we call

hyper filtration and so therefore this

may allow for some compensation after

removal of a kidney

whether or not this occurs in other

markers models of acute kidney injury or

other patients admit admitted to

hospital with acute kidney injury

for example due to sepsis we dont know

and as mentioned this may relate to

hyperfiltration of the remaining kidney

maybe it also relates to changes in

uremic toxins were not certain

animal studies also dont support the

intact nephron theory when were talking

about acute kidney injury for example

in some cases uh transporters there may

be increased expression for example if

you do a nephrectomized rat you get

an increase in the expression of some

transporters

there may be an overall decrease in

clearance because of the decrease in

nephron mass

but there is a lack of proportionality

for example for drugs that would be

substrates of these transporters

and sometimes

some of these changes may rapidly

resolve

so this may relate to hyperfiltration of

the remaining

nephrons

in some cases there may be decreased

expression

in some cases we get differences in

expression depending on what the cause

of acute kidney injuries

for example

nsaids which can cause acute kidney

injury may protect against changes in

organic anion transport

down regulation

but if you look at an ischemia

reperfusion model of nephrotoxicity

then oct may be downregulated

and some of this may perhaps relate to

hyperfiltration of the remaining kidney

really more data is required

how do we quantify

gfr in patients with acute kidney injury

as already mentioned we cant use the

regular formulas because of changes in

creatinine

so if we go back to this slide

ecretin ecreatinine clearance and egfr

based on a single creatinine and the

assumption there is that youre in

steadystate conditions and were not

with acute kidney injury so you cannot

use them

you can do a

measured creatinine clearance and this

has actually been done by a number of

clinical groups but also research groups

for example if youve got a person

intensive care whos catheterized you

could do maybe an eighthour urine

collection

and estimate the creatinine clearance

based on that

you can also go to measure gfr

for example send them to

in my hospital stand up to nuclear

medicine where they may give dtpa or

inulin or mag

and

this can be used to measure the gfr

uh at that time

of course though with acute kidney

injury there can be changes so you need

to have a really good reason for

measuring that

and acknowledge that

tomorrow

maybe even six hours later the gfr may

have changed

so in conclusion

this is a summary slide showing how

we may get changes in patients in

pharmacokinetics and patient patients

with either acute kidney injury or

chronic kidney disease

ive gone through most this information

so im not going to read it to you now

im presuming you can pause the

slide

if youd like to read specifics into

these

ive also added the impact of

doing kidney replacement therapies or

dialysis

although that was covered by another

talk

so in conclusion acute kidney injury and

ckd impact on the pharmacokinetics of

many drugs but data are limited for many

drugs and also many scenarios

despite these changes it is also marked

into individual variability and so it

really does

complicate the development of dosing

guidelines

whether based on something at the

institutional level or suddenly the

patient level

the failure to properly account for the

effect of kidney disease when

prescribing

and inadequate monitoring can predispose

our patients to treatment failure

adverse drug events

which we want to avoid

thank you