and so as mentioned theres two forms of

im going to talk about each of these in

turn turn now

okay turning now to pharmacokinetics and

chronic kidney disease

this is the overview of the topics that

well be discussing during this

presentation

its very necessary for us to be alert

for impaired kidney function and to be

able to diagnose it

this is important for a few reasons one

is it can influence treatment decisions

but number two is a chronic kidney

disease is generally an asymptomatic

disease until the very end so if were

not doing blood tests to measure kidney

function we may not know that someone

has impaired kidney function and

therefore we dont know to a dose adjust

how do we diagnose chronic kidney

disease

this is how we stage chronic kidney

disease

we have stages of one through to five

whereby five is the worst and one is the

best

two factors are considered when were

staging chronic kidney disease one is

the presence of kidney damage this

relates to whether or not we see

proteinuria or hematuria

on testing in the urine and the other

relates to renal function which is based

on here the egfr

which is mills per minute for

meters squared

so we can see here that as

renal function drops

the stage increases

is the impact of chronic kidney disease

on pharmacokinetics

so the first principle well be talking

about is absorption

when were thinking about absorption

were thinking about

how does

absorption in patients with chronic

kidney disease

vary compared to the healthy individual

without kidney disease and the second

relates to how it compares within

patients with the range of chronic

kidney disease

whether it be stage five or stage one

and we know the drug absorption can be

highly variable in all of these cases

theres a lack of consistency between

data thats identified in different

studies

its commonly thought though in that

absorption will decrease in patients

predominantly when there is edematous

states

so if you have edema peripheral edema

then you may also have marked edema

within the gut wall and this may impact

on drug absorption

but the data has actually been quite

conflicting on that and certainly its

not um always reliable

theres been even some cases whereby

this is in animal and human data whereby

drug absorption may actually increase

and one of the theories for this may be

is that edematous states or some other

damage to the gut wall

may impair the active transporters and

enzymes that are present there which

contribute to the lower bioavailability

of some drugs

so in this case uremia fluid absorption

may impact on usual protective

mechanisms

what about volume of distribution well

volume distribution varies not only with

body mass but also with body composition

this relates to water or adipose tissue

so changes in volume distribution

probably depends on the drug that youre

thinking about

we know that in advanced chronic kidney

disease there is risk of fluid retention

hypoalbuminemia and both these factors

can also be contributed to by decreased

protein binding which may relate to

accumulation of uraemic toxins

the presence of severe edema on the

impact of volume distribution is fairly

inconsistent and this may relate to the

fact that were looking at different

drugs drugs with different physical

chemical and pharmacogenetic properties

so there is no clear rule

but probably what does happen is

patients which are more hydrophilic in

nature are more likely to have an

increase in their volume of distribution

because there is some water retention

however even in dialysis patients the

interdialytic weight gain that occurs is

relatively small compared to the overall

body

volume and therefore this tends to have

a relatively small component

some patients

can have sarcopenia which means general

muscle wasting and this is a particular

problem with patients with advanced

chronic kidney disease and in that case

there may even be a decrease in the

volume of distribution

so it can be concluded that volume

distribution can change it can go up and

it can go down and that depends on the

drug

and im sorry that i cant give you any

um more reliable

predictions around that

clearance in chronic kidney disease well

ive said this a couple of times and

ill say it a few more times this is the

main pharmacokinetic change that occurs

in patients with impaired kidney

function

we know that multiple conditions can

cause chronic kidney disease and were

starting to learn a bit more about how

the different conditions may actually

impact on the changes in clearance

chronic kidney disease we generally

consider that the decrease in gfr

relates to whats called nephron dropout

so its not that a certain number of

nephrons are functioning to a lower

level

its actually a certain number of

nephrons have died so there is sparing

of nephron function

and that these things are all

proportional

so this is whats been called the intact

nephron theory

so

ive told you before about how you can

get metabolism and active secretion at

the kidney its

always been put forward that all of

those functions are in proportion to gfr

because we have an intact nephron

were going to talk more about that and

some of the limitations around that

um

because its more complex than that in

reality

i showed you this slide before

which is a very important one and in

particular if i can draw your attention

to this point here about how total

clearances relates to the sum of

clearance from other

processes or organs including that of

the kidney

well come back to that again so how do

we quantify gfr ive already told you

that gfr is the most important measure

of kidney function thats how we grade

kidney function

and if we think that

through the intact nephron hypothesis

that all functions of the kidney are

proportional to gfr then surely it is

very important for us to understand and

quantify the gfr if were going to be

using this to dose our medicines

there are multiple methods by which we

can quantify gfr

the vast majority of these are all based

on serum creatinine concentrations and

theres three ways that we can do that

one is to measure

clearance and this is made done

through a hour urine collection

well talk more about each of these as

we go through the next is what i call

and many others call the estimated

creatinine clearance

which is actually the and

clearance based on the cockroft gold

formula

which is known love to many of us

and again well talk more about that and

the most common method of merging or

quantifying gfr is the egfr ckd epi

as shown here

we can also do a measured gfr

this is a gold standard this is where we

would inject something into a person

and then we measure its clearance

through the kidneys

and theres also a new

guy or girl on the block called

systatincy this is a relatively newer

test which is now available to help

quantify gfr

im not sure if this is currently

available where you are from my

perspective here in australia it is

available but its largely based on

limited circumstances i would need to

contact my laboratory specifically to

order it its not part of a routine

panel

lets talk about each of these

so when we think about serum creatine

based formulae

we know here that

the premise of this is a

excretion is proportional to kidney

function so if kidney function

halves then were going to have a

doubling of creatinine

the problem with this though is that

creatinine production is proportional to

muscle mass so there are some

individuals whereby this would not be

helpful for example if youve had an

amputation or youre um or youre in a

wheelchair so you have whats called

disuse atrophy of the muscles uh

particularly in the legs then because

youve got a lower muscle mass youre

going to have a lower production of

creatinine and so many of these formulas

will be wrong

on the other side for people who have a

higher amount of muscle mass and this

may relate to obesity because more

muscle is required

for mobilizing but particularly for

people who build muscles

with their high muscle mass it means

that theyve got a higher creatinine

concentration and this doesnt

necessarily mean

that

they have impaired kidney function if we

look at a blood test

there are a number of people whereby

these formula arent certain were going

to talk more about those in a moment

lets start first with the hour

collection this was always the gold

standard prior to the publication by

cockroft and galton 9 and a few

others around that same time

this is where we as mentioned you need

to collect hours worth of urine and

this is difficult because uh all of us

past urine at different times its very

hard to say that any particular time of

the day we would most consistently pass

urine and therefore thats when we would

start a hour collection

the most consistent time when someone

would start would pass urine is in the

morning when they wake up after sleeping

and so if you are doing a hour urine

collection unless the patient is

catheterized then its best to start the

next day in the morning so when they

wake up in the morning they empty their

bladder at in the into the toilet and

then they start collection of the

hour urine collection that can

continues until the next day

the problem with this process is that

that is errorprone

quite often samples are missed even

with very careful supervision

also theres a time delay until you get

the results it takes at least hours

for the samples to be collected and then

after that the sample needs to be

processed by the laboratory calculations

performed

and its inconvenient

youre largely telling patients that

they need to stay in hospital stay at

home so you can measure this so that

because they dont want to have to walk

around

the streets carrying a large urine

collection bottle

creatinine clearance by this method also

slightly overstates gfr

because there is some active secretion

of creatinine in the proximal tubule

so the next one is cockroft gold uh

formula or ecretin clearance its

called the ecrating clearance because

the gold standard upon which cockroach

got was based was a hour and

clearance so its really just estimating

the creatine and clearance of that

so thats important because like i said

before

um this will slightly overstate gfr

because of the active secretion of

creatinine into the proximal tubule

this is recommended for many drugs and

its something that a lot of us have

been taught as part of our education but

a problem with this is that firstly it

requires us to do a calculation and when

youve got humans doing calculations

theres always a risk of error

the other issue is that since 00

theres been a change in the way the

assay has been performed and this was in

an attempt to standardize the assay

across the world

and in doing so its its now reduced

the accuracy of the predictions by

cockroft gold because were now talking

about a slightly different

assay

its probably only changed estimates by

about 0 to 0 percent but it is still a

change

and the next question is uh this is the

formula up here what body weight do we

use do we use actual body weight do we

use lean body weight ideal body weight

this can be very important because some

people are

quite slim some people have more

weight to them and that may not all be

muscle weight

or water weight

and and so therefore

we need to consider which body weight to

use

ill go through that in a moment

but its important to remember that all

of these things are only estimates this

is a publication from 009 which

compared the cockroft gold egfr

to inulin gfr which is an example of the

measured gfr that i told you about

before

and while we can see theres very

clearly

a

proportionality there a correlation what

we can see is a lot of scatter of the

dot points so its not very accurate

so if we had someone with a measured gfr

of 90 we may get a cockroft gold

gfr which is very easily between 0

and 0

so theres a lot of error within these

estimates based on cockroft gold it is

not a pure measure of kidney function

the next one is our egfr or ckd epi as

you know we love this for so many

reasons its automated whenever we order

a creatinine we automatically get back

an egfr

therefore its readily available

and its commonly used for all of these

reasons because its very practical

the issue with this is its not formally

recommended for many drugs

most drugs were developed in the day

when cockroft gold was used and

therefore that is a recommendation of

what we use

and also doesnt incorporate body weight

or height at all this is produced by the

laboratory they have no idea about the

body status

or morphology of our patient we need to

know that and so then we need to

consider if we should adjust this gfr

for some people who have extremes of

body size as you can see here egfr is

indexed to a body surface area of

meters squared

of which not not many people in the

population are that size theyre

actually larger

and well talk about how we respond to

that in a moment

similarly

as shown with ecrating clearance egfr

also is a very poor estimate of a

measured gfr this is showing estimated

gfr on the xaxis and on the yaxis is a

measured gfr in both cases theyve

adjusted for body surface area

so it takes away the factor of the

patients size or morphology

and we can see here that ideally it

would be a flat line of zero but instead

were getting lots of spread of data so

again

someone with a measured gfr of

say 0

then the estimated gfr could be anywhere

between

minus 0 or plus 0

from that

so

there is a lot of

error within that as well

i mentioned to you about how a problem

with the egfr is we dont know the

weight or height of um the essays that

the laboratory doesnt know the weight

or the height this is where its done

our job as clinical people

to be able to adjust that if needed

so if we look at the original ckd epi

publication it was done mostly in

patients who are all less than years

of age and their body surface area was

9 to 9 meters squared with a bmi of

to

kilos per meter squared im sorry i just

realized that um i only have them uh in

metric units

apologies

and also weight and height

of

[Music]

0 centimeters and um at a weight of

kilos so 0 kilos would be

about 0 pounds

uh and so

the i dont have that many patients who

who fulfill these criteria most are a

bit taller than that and certainly many

are

higher weight if i look at these numbers

these dont apply to me im much heavier

and are much taller than this and so

therefore an egfr may not be fully

reflective of my kidney function but

also that of our patients as well

and so its possible to adjust for the

egfr for our patient using this

deindexing formula which is simply

where the patients gfr is

egfr

times by their body surface area divided

by

this is something that i not uncommonly

do this calculation

to work out a better estimate of their

gfr

when im considering dose adjustments

this is a summary table which talks

about how different patient

characteristics may impact on the ecrat

and clearance or the egfr

from a paper that we wrote a year or two

in the journal called the australian

prescriber

and it shows how in patients with

reduced gfr or higher body surface area

older age younger age obesity

or

perhaps particularly more lean it talks

about which of these two formula may be

more accurate or less accurate

this is largely based on limited data

but it gives an indication

but in general as ive already shown you

both egfr and ecretin and clearance

have so much error compared to

the measured gfr

in general i think it doesnt matter

but what i think is more important is if

someone has a particularly high bmi for

example a weight greater than 0 kilos

which is about 0 pounds approximately

or a bmi which is less than 0 kilos

which is about 0 pounds

or kilos per meter squared then we

need to consider other alternatives and

thats where for e um gfr we do a

deindexing of the gfr

and for ecrating clearance we use the

adjusted ideal body weight

or if theyre lean then we use their

actual body weight

and again we deindexed egfr

so different ways that we can do this

depending on what you prefer

but this is a rationale for why we would

change these

measurements

how we would deal with these changes in

patient characteristics

and why in general i think it doesnt

matter which one you choose because

theyre all a bit wrong

remember this slide where i spoke about

how you have three different types of

drugs we spoke about a few different

examples and how they change with gfr

sorry how about how a change in gfr

changes a drug clearance

lets talk more about this in the

context of chronic kidney disease

because this looks like a very stylized

and ideal representation

um ive changed that picture slightly so

that ive normalized them all to a

single point here of a hundred percent

but you can and im sorry that the color

is different but we can still see here

this is the one which is proportional to

gfr

this is one which has mixture of kidney

and

nonkidney clearance this is a example

of a drug that has complete kidney

clearance

lets look at some real data to see how

this reflects real life

this is showing the influence of

creatinine clearance on meripenem

clearance ameripenem as you know is a

its an antibiotic thats largely rent

thats completely randomly eliminated

and we can see here that these data

points although theres a bit of

variability or spread we can see that in

general creatinine clearance is

completely proportional to meripenem

clearance

so thats consistent with the line that

we showed here which is the gray one

thats what wed expect

then if we look here at uh changes in

and clearance with ciprofloxacin

again this is an example of a drug where

i said its a mixture of

hepatic and renal clearance so about 0

hepatic and about 0

renal

and we can see here again although

theres a bit of spread and variability

of the samples again it looks like

this is performing as we would expect

now lets look at roxithromycin

roxythromycin is an is a macrolide that

we use very commonly here in australia

im not sure its as common in the us

but its a well tolerated antibiotic

which has few drug interactions

only about 0 is excreted in the urine

therefore its a drug thats largely

hepatically cleared so we would expect a

straight line

now we can see some variability here but

i think it really does look like there

is a decrease in kidney function

that is a the kidney function decreases

and there is a decrease in drug

clearance

so this is unexpected

why is that

maybe this only applies to oxythromycin

though maybe its a an aberrancy

actually its not

and if i show you this figure im sorry

its the same figure that ive just

shown you but turned around mirror image

whereby this is decreasing kidney

function

and this is changes in metabolic

clearance

and we can see here that for a lot of

different drugs this is data based on a

combination of animals and humans

whereby through

pharmacometric processes and elemetric

scaling theyve been able to come up

with a with a line that

summarizes how these drugs clearance

changes with impaired kidney function we

can see here that for a whole range of

drugs there is a decrease in kidney

function so there is a decrease in

nonrenal clearance with decrease in

kidney function

now each of these drugs has been chosen

because its a probe for different drugs

so theophylline for example is a is a

professor cytochrome p0a

razorglidasone is a probe for

two c boston tan is for two c9

omeprazole is for c9

befuralol is for d and it does lamp

the a

so this is showing that for a number of

different sorts of cytochrome p0s this

effect can occur

for some for example omeprazole shown

here which is c9 we can see that

metabolic clearance is decreased to

of or lower than percent of what it

would have been otherwise

whereas some of these other drugs we can

see that they still have more than 0

percent of their metabolizing capacity

so theres a lot of variability

and this is just based on those

particular drugs

and it doesnt necessarily mean that all

drugs metabolized by those cytokine

p0s will change to the same extent

so this is surprising its not predicted

why is this

well if we go back to this figure that i

showed you here it probably relates to

this

circulating uremic toxins that inhibit

these enzymes

and impact them on drug clearance

so this then raises a question

perhaps with higher amounts of uremic

toxins we have more severe inhibition or

more marked inhibition of the liver

enzymes

thats kind of what were seeing here as

a kidney function gets worse metabolic

clearance gets worse

well thats enzymes what about other

drugs or other processes this is looking

at the disposition of fexofenidine the

antihistamine in patients who are either

without any kidney function or with

endstage renal disease or instage

kidney disease and we can see here that

there are changes also with affects of

benign

what are the pharmacokinetics effects of

phenidine well its not metabolized but

its a substrate of transporters p

glycoprotein and opv

these are both active transporters their

role is to

reduce absorption of drugs so they sit

on gut wall and they extrude the drug

before it gets absorbed theyre also

involved with the excretion of the drug

in the kidneys and also in the biliary

system

and what we see here is that patients

with endstage kidney disease have a

high concentration that persists for

longer

if you prefer seeing a table with

numbers this is what we see

noting that normally in health

bioavailability is about percent of

this drug

so therefore factors at impact and

bioavailability would increase the

concentration and this is what we see so

the cmax has increased fold

the halflife is times longer

we have a halving of the clearance and

the auc is increased by volt

so this means to me that we most likely

have an increase in absorption

so that may mean that those transporters

are not working very well

and a prolonged elimination halflife

which is due to a decrease in clearance

and this must relate to

due to inhibition of these transporters

further proving the fact that

i was supporting the fact that endstage

kidney patients have used uremic toxins

which are causing changes in function

this is where

the researchers again by tom nolan and

colleagues

they obtain bloods

a blood sample from patients with

endstage kidney disease and they

incubated it with rash hepatocytes and

enterocytes and looked at changes in

protein

expression

for pe glycoprotein

opa

and cytochrome p

a

and we can see here that there can be an

increase in pgp or a decrease in pgp

there can be a decrease in c

there can also be a decrease

in oat pa

this shows that

uremic toxins

are having an impact on

on protein expression as well

and and that can be contributing to some

of the changes that were seeing

and the mechanisms of this as i

mentioned before were thinking about

this is the lumen of the intestine and

thats the interest site so drugs can

enter the intersociety through diffusion

or active uptake bioretransporter

once in the interest site it can be

metabolized

or it can be extruded by the pgp

or it can then enter the circulation so

this is part of our process

of um these processes contribute to

to

bioavailability

here in the portal circulation they can

be uptaked by the hepatocyte to either a

transporter and then within the

hepatocyte there can be metabolism where

they can then be fluxed or they can be

excreted into the biliary system so we

can see here that theres multiple

transporters and enzymes which may all

be impacted on by uremic toxins and its

these multiple impacts

that can change the pharmacogenetics in

patients with kidney disease

but ultimately what we would see is

if there is less of the pgp then well

have a high concentration

in the interest site if there is less

cytochrome

p0 activity again we have a higher

concentration so we get a relatively

increased

dose due to the decrease in

bioavailability

and we get impaired clearance as well

what may also be fascinating we dont

have a lot of information on this is

that the etiology or the cause of the

kidney disease may also have an

important impact on kinetics

for example studies were done that

showed that if youve got chronic kidney

disease due to a tubular dysfunction

then you may have

less

clearance of drugs such as ambicillin

and caphylexin than you would for

patients with the same gfr who have

glomerulonephritis

so what this means is looking at two

patients who apparently have the same

gfr

depending on the cause of their kidney

disease you may get differences in

clearance

and this relates to

the active transporters so as we know

this is the nephron where we get active

drug secretion proximal tubule and

active drug reabsorption in the distal

tubule

we compare these three drugs

benzoyl penicillin

um

0 to 0 of clearance is based on oat

the organic anion transporting

polypeptide which is found in the

proximal tubule

and so if youve got a tubular

dysfunction

then you may

then this may impact on the secretion

same applies for metformin its um

actively secreted

by the organic cation transporter and as

mentioned to you earlier

much of the clearance is based on that

so when we look at this what this means

is that

we have very high total clearances of

both benzoyl penicillin and metformin

because of these active secretion

pathways even though the drug is totally

cleared by the kidney in that context

and so

changes to tubular function may then

impact on clearance and

it doesnt relate to the intact nephron

hypothesis

fluconazole is interesting because there

is some active reabsorption in the

kidney so to an extent we need to

decrease the dose of decreasing kidney

function

but then it gets to the point where we

need to stop decreasing the kidney

function because a decrease in nephron

mass is also associated with a decrease

in the amount thats being reabsorbed

and so its this reabsorption that

maintains the blood concentration

so

if were not getting reabsorption then

we need to give more drug relative to

gfr

and thats where the dosing of

fluconazole can be interesting

theres other examples as well

where

there are changes in pharmacokinetics

with impaired kidney function and we

need to think about how we would make a

dose adjustment this is the example of

dihydrocodeine

the blue line shows normal kidney

function and the black line shows some

with advanced chronic kidney disease

so we can see here that there is a

higher cmax

and a slightly longer halflife

this largely relates to the fact that

there is inhibition of sip d and a

activity with uremia

which is what causes these changes

so how would we dose adjust

the prescribing of our dihydrocodeine in

our patients

we would

this is not such a

large change in cmax the main issue

relates the longer halflife so we could

give the same dose but we would do it

less often

and then were at less risk of

accumulation of dihydrocodeine and the

complications including sedation

but if we compare it to repaglinide

which is used for the management of

diabetes we can see here that theres

some arc differences the blue line again

shows a person with normal kidney

function but the black line shows a

person with advanced chronic kidney

disease

and what we can see here is that there

is almost a doubling in the cmax

and again we get a slightly longer

halflife whereby it persists

oral repaglinite is a substrate of sip

a and c but also one of the

organic anion transporting polypeptides

so its got multiple factors whereby

uremia may impact on its kinetics

so how would we dose adjust for

paglinage

well we could probably give half the

dose and maybe we can give it half as

often as well

we need more information on that but we

can see here just on those two examples

that very different

changes are acquired in the dosing

regimen

for them

if youre prescribing it to a person

with chronic kidney disease

so

what does all of this mean that these

representations that ive shown you on a

number of times really are probably an

oversimplification this formula doesnt

apply because if we cut out

the kidney function

we know that there may also be a change

in hepatic

clearance and maybe others as well such

as

transporters and this one also doesnt

work completely because those with the

flat line there may actually be a change

in clearance as well

maybe its close enough in most cases

and it depends on the particular drug

i dont think this is a reason for us to

stop teaching our students about these

these principles because i think theyre

important principles because were still

trying to understand the clinical

significance

um and the generalizability of these

changes

in uremia

this is just to show some data from

metformin because in many cases it seems

to be a reasonable

estimate this shows decreasing gfr

decreasing metformin clearance as ive

already told you you can get some

massive clearances with metformin and

its all through the kidneys

um 00 mils 00 mils

meals per minute and this is due to the

active transporters and this would make

you think that with decreasing kidney

function there is still that

proportionality between

[Music]

drug clearance and gfr

and so maybe the intact nephron

hypothesis does apply to metformin

so why is all of this important well

what i think ive shown you is there are

some unpredictable changes in

pharmacogenetics and chronic kidney

disease

and the extent of this depends on the

severity of the ckd and also the drug

theyre interested in

while ive shown you a number of

examples of drugs which are notable and

interesting

and general data are limited so broader

implications of this is really poorly

defined at this point

and its particularly complicated for us

when we think about new drugs because

theres such limited data

i think also some of these factors not

commonly considered by clinicians or in

dosing guidelines

particularly when there are guidelines

which are talking about empiric dosing

whereby we estimate what dose to give to

a patient

in the absence of pharmacogenetic data

at the moment its hard difficult to

know exactly how we can do it any better

because we cant always predict which

drugs will be affected by nonrenal

pathways and advanced kidney disease

but what it is is it does do it reminds

us that we should be monitoring our

patients closely

even if we anticipate

that there wont be other nonrenal

changes to kinetics

in advanced kidney disease

so when prescribing to patients with

chronic kidney disease

so dose adjustment ive already

mentioned that the purpose is to reduce

adverse events whether it be to sub or

super therapeutic drug concentrations

a common or conservative approach in

most cases with kidney disease is to

start low and go slow and i think thats

appropriate

then the rate of dose escalation really

depends on what is the clinical target

that youre aiming for its blood

pressure or hbac

then these are often delayed in their

response so we need to change our dosing

over weeks or months

this is probably okay in many cases

and will avoid adverse drug reactions to

super therapeutic

doses

so when does a change in the

pharmacokinetics process

prompt dose adjustment

so ive shown you about how you can get

changes in clearance when is it that

wed say that the clearance is important

its commonly been quoted that if

clearance changes by 0 you should

consider a dose adjustment

and thats always been considered

conservative the first time that was uh

described to my knowledge was by a

pharmd

dr levy uh in about 99

and it was an unreferenced

statement

he was considered very smart

and

and quite accomplished so its probably

true

but the point was that

we should consider dose adjustment at

that point not that we need to dose

adjust because dose adjustment largely

depends on the drug were using in its

own toxicity

it also depends on the drug so it

relates to the drug but also depends on

the duration that were dosing a drug if

were anticipating that were going to

be dosing a drug for a relatively short

duration then the likelihood that it

will accumulate to toxic levels is

probably low

and therefore we may not need to over

complicate our decisions around dose

adjustment

and a draft fda document suggested that

if theres a substantial effect on

pharmacokinetics then we should consider

a change in dose and they

suggested here that an area under the

curve increasing by at least 0 or more

likely a hundred percent compared to

healthy individuals would be an example

of when wed consider dose adjustment

other considerations a slow interest of

iterative approach that i mentioned

before start line goes slow doesnt work

for all drugs so for immunosuppressive

or antieffective so we want the drug

effect now

and we need as soon as possible to be

able to preserve organs preserve life

and to prevent toxicity

[Music]

and we know that many cases whereby

antibiotics have been inappropriately

dosed to patients with impaired gfr

largely because

of uncertainty about the best way to

dose

so for some of these drugs underdosing

may be as bad as overdosing and this is

where therapeutic drug monitoring has a

very

clear role as im sure everyone is aware

so for conclusions about

pharmacogenetics and chronic kidney

disease we know that changes are

documented for absorption distribution

metabolism and excretion

and the extent of this varies between

patients drugs and severity of chronic

kidney disease

more data are required to better define

these changes

and careful dose adjustment may be

required

and as mentioned also these

relationships only apply at steady state

which is a chronic scenario

what this means here is that similar to

talk about steady state conditions

for uh drugs

uh much of the discussion weve already

had only applies if youre at steady

state conditions for creatinine and the

kidney function

and this doesnt occur with acute kidney

injury or its not the case for acute

kidney injury and so lets now talk

about that because thats another level

of complexity

thank you