Patrick Murray, MD
Dr. Patrick Murray is an attending nephrologist and Director of the Acute Dialysis Unit at the University of Chicago Hospitals, Chicago, Illinois. He attended medical school at University College Dublin, Ireland. He completed a residency in Internal Medicine at Hennepin County Medical Center in Minneapolis, Minnesota. He then completed fellowships in Nephrology, Critical Care Medicine, and Clinical Pharmacology at the University of Chicago Hospitals. He is an Associate Professor, and Director of the Hospitals' Nephrology fellowship training Program. He conducts clinical research in the prevention, detection, and management of acute renal failure in the ICU. He is Editor of a forthcoming textbook entitled "Intensive Care in Nephrology", which will be published in 2005, and is co-edited by Professors Hugh Brady and Jesse Hall.
Introduction

Dr. Murray: Because of the practice of nephrology in the ICUs, there are a variety of things that we need to know to practice effectively in this environment. And I'll tell you, that because intensivists have been making such progress with treating respiratory failure, treating sepsis to a lesser extent, and treating acute coronary syndromes, their attention is increasingly on acute kidney injury as an area of frustration, because it's the one thing they cannot fix. And in a lot of closed ICUs it's the one thing that they don't take care of themselves. So, I think if we don't know a lot about the literature in critical care and don't know what they're talking about, they will eventually stop asking us to come and see their patients, which I think is the reason to know this material more so than the boards.

Having said that, you will have noted in the introduction that there is a cross-disciplinary critical care part of the boards, so there will be some questions on that basis.
What we're going to talk a lot about is issues to do with management of severe sepsis, septic shock, and the relationship to septic acute kidney injury. We'll talk about hemodynamic management including early goal-directed therapy and choice of vasoactive drugs. We'll talk about antiinflammatory therapy and some issues with regard to steroids and activated protein C. I'm going to talk a fair bit as well about acute lung injury, lung-kidney interactions, impact of lung-protective ventilation, some interesting new data about fluid management, and a little bit about pulmonary effects of acute kidney injury.
Mortality

So first of all, why is this relevant? This slide which is now getting pretty old is still accurate, unfortunately. If you have dialysis-requiring severe acute renal failure in the ICU setting, the mortality is still a minimum of 50% but often up to 80%. The other thing that of course has been of longstanding discussion is - are they dying WITH acute kidney injury or are they dying OF acute kidney injury? And the answer is, undoubtedly, both. There is evidence that acute renal failure per se increases mortality independently, but it's also true that in this setting of dialyzed acute kidney injury, in those who are in the ICU who just have acute renal failure, you can see the mortality can be as low as 40% in this review summarizing other studies. Of course, those people don't get to be in the ICU anymore. But if you throw in a ventilator and some pressors, so in other words respiratory failure and cardiovascular failure, this is quickly where you get into the 60% to 80% mortality.

Effects of renal function changes in sepsis

Many of you may have seen this study, but I think it’s very enlightening and it shows just how important the kidney is as a marker of how critically ill patients are doing. Every surgeon, to their chagrin, every intensivist, and every consulting nephrologist, know that when the kidneys are getting worse in critically ill people, bad things are happening and patient mortality is going up, but this study nicely demonstrated it.

The study looked at the control arms of two large sepsis trials—one was actually the original activated protein C trial and there was another inhibitor trial for sepsis that the control arm was used for. And what they noted, first of all, in looking at the first 24 hours of the patients’ enrollment in the study, was that, first of all, at baseline, the mortality of 28 days with sepsis was lowest in those who went in with the lowest serum creatinine. And there appeared to be some relationship between the entry creatinine and mortality going up, up to a creatinine of 3.4, at which point there ceased to be a clear relationship. I don’t think that’s the major point of this study.

The major point actually, was what happened after 24 hours of the best management they could do in this control arm to the renal function. And if they did everything they could hemodynamically and with therapy of infection, and the renal function actually started okay and stayed okay, the mortality was 20%. But if renal function started normal and became abnormal despite the therapy, you can see that patient mortality doubled in this study. Similarly, if they started with more advanced renal failure going into the period and improved to a creatinine less than 1.2, the mortality stayed less than 20%. If they were stuck and did not improve, you can see the mortality was higher. And if they got worse it was a disastrous sign: the mortality was 60% in those who started with renal failure and who, despite resuscitation continued to have renal failure. And the trend actually continued in those who had even more severe renal failure, as you can see here.
Severe Sepsis Therapy

- Prevention of nosocomial infection
- Timely, effective antibiotic therapy, and radiological or surgical intervention
- **Hemodynamic management**
  - Corticosteroid therapy
  - Recombinant activated protein C therapy
  - Intensive Insulin therapy
  - Mechanical ventilator strategy
  - Renal replacement therapy

**Severe sepsis therapy**

So what are you going to do about this? Of course you are not actually always being asked to see these patients at this time. Many of you admit patients yourselves to the ICU, and you may be managing patients like this at the beginning, but what are the kinds of things that should be done early on to treat someone with severe sepsis? And I'm not going to touch on some of the obvious things. It has been well shown, for instance, that earlier antibiotic therapy improves outcome in patients with a variety of infections, which is common sense. I'm going to get to some of these other issues later, but I'm going to focus on hemodynamic management for now.
Septic shock pathophysiology
Those who have septic shock, which is sepsis with systemic hypoperfusion usually signaled by hypotension, have a variety of causes for this. First of all, because of venodilation and capillary leak, all these patients present with hypovolemia, and they may just look like they have hypovolemia until you have volume-resuscitated them. At that point, they will usually manifest persistent hypotension despite a decent fluid challenge, and in those patients the cause will be a combination of the fact that although septic patients usually have a normal or elevated cardiac output, it's not as elevated as it needs to be to make up for their systemic vasodilation, so they have relative myocardial depression. Then of course everybody knows that they have, in many cases, systemic vasodilation because of vasoparesis. This, all being in the face of increased metabolism, results in tissue hypoperfusion.
Pharmacologic Approach to Optimization of Renal Perfusion

- 1) CO: fluids, inotropes to achieve “adequate” cardiac output
- 2) MAP: fluids, inotropes, pressors targeting MAP 60-80 mmHg (?)
- 3) Renovascular resistance: renal vasodilators
- 4) Corticomedullary blood flow distribution: renal medullary vasodilators
- 5) Renal tubular oxygen consumption: diuretics (furosemide, mannitol)

Pharmacological approach to renal perfusion
This is one way to think about it. If you are being asked to see a patient with renal insufficiency, how can you optimize renal perfusion, to at least take that part of the renal failure out of the equation? And I like to think about it in terms of 5 levels of renal perfusion. First of all, we’re going to concentrate on optimizing cardiac output. We’ll then move on to discuss perfusion pressure, renovascular resistance, distribution of blood flow within the kidneys, and manipulation of oxygen consumption. I should say on these latter two points, that nothing has been shown to favorably alter intrarenal blood flow distribution and improve renal function in a clinical setting. Similarly, although diuretics are theoretically attractive to decrease tubular oxygen consumption in the loop and prevent renal failure, they have never worked prophylactically or therapeutically. I’m sure Dr. Bonventre will cover this in more detail. So I’m going to concentrate more on the systemic perfusion aspects.
Starling curve for stroke volume
This is a standard Starling curve, whereby if you raise left atrial pressure from say 10 to 20, CVP would be a lesser number than this but would show a similar trend - you should have a response of increasing stroke volume and cardiac output. And if you do not, if you have a flat response, the differential is, that either the patient is not yet full, for instance if they have diastolic dysfunction and the pressure does not reflect a full left ventricle, or they have myocardial depression, which could be because of something like chronic CHF or acute septic myocardial depression. As usual, nephrologists will always feel, and in general find when they examine this, that fluids are the best way to treat or in fact prevent most kinds of acute kidney injury, as again I'm sure Dr. Bonventre will reinforce.
Septic ARF Prevention/Rx: Fluids

- No difference in RRT Days (0.5±2.3 vs 0.4±2), new organ dysfunction, survival with saline vs albumin in 6997 pts
  - SAFE Study Investigators: NEJM 2004;350:2247-56
- Albumin prevents ARF in cirrhotics with SBP
- Gelatin-based colloid not hetastarch prevents septic ARF

Septic ARF prevention
Just a couple of points from recent literature. One of the discussions has always been - does it make a difference if the fluids are crystalloids or colloids? And it turns out that in a large Australia-New Zealand trial, the SAFE study, which was an extremely well done and, as you can see, extremely large trial, there was no difference in outcome with saline versus albumin in treating critically ill patients. But in addition, it should be noted for our purposes, there was no difference in the number of days of renal replacement therapy or new organ dysfunction in those who got crystalloid versus colloid. You already heard in Dr. Kupin’s presentation that one of the other examples where giving fluids prophylactically prevents renal failure was in cirrhosis, where giving albumin with antibiotics versus just antibiotics prevented or decreased the rate of developing acute renal failure in cirrhotics with spontaneous peritonitis. Of course, it would have been nice here if there would have been a third arm with crystalloid so we know if albumin was relevant. There is an increasing literature, as you saw again in one of the earlier cases, suggesting that hetastarch seems to increase the rate of acute kidney injury in critically ill patients. This is just one example compared to another gelatin-based colloid, but there are now several examples saying that hetastarch is probably not a good choice as a volume expander in critically ill patients. It seems to increase the risk of renal failure.
Principle of fluid challenge

What remains an area of difficulty of course is, when do we stop giving fluids? Again, as nephrologists, unless somebody is frankly developing problems with volume overload, pulmonary edema, etc., it's always going to be better for the renal function in theory to give more fluid rather than less. But of course that's not always going to be without a cost. Although there are tools being developed by people like Dr. Magder to determine when you have gone from volume-responsive hypotension to volume-unresponsive hypotension, these are not really validated for clinical use.
Pulmonary Artery vs. Central Venous Catheter Monitoring

- No improvement in survival or renal function in RCTs in.........
  - **Acute Lung Injury:**
- .......or in a recent meta-analysis


**Pulmonary artery vs. CV catheter monitoring**

So what many of us are relying on is a combination of clinical examination following trends, and also looking at some kind of invasive hemodynamic monitoring for someone with worsening renal function. And it should be noted that there are now more than enough trials to say that it's probably no longer justified to ask for a pulmonary artery catheter as opposed to a central venous catheter to sort out hemodynamics in most critically ill patients. There have now been enough randomized trials in acute lung injury with shock, but also in acute lung injury in whom shock was excluded. We'll actually talk about another aspect of this - large fluids and catheters treatment trial - done by the ARDSNet group to sort out issues of wet versus dry. That's what we're going to detail, but I will just summarize their recent study in PA catheter versus CVP: there was absolutely no benefit in terms of survival or organ function in putting in a PA catheter compared to a CVP line, but there were more arrhythmic complications with the PA catheters. I think that has pretty convincingly demonstrated that it should not be a routine approach. Similar results have been shown in congestive heart failure, high-risk surgical patients, and a meta-analysis of several studies.
Rivers study
With a CVP line, another study I think many of you are familiar with, is this study by Rivers, which validated the approach of early goal-directed therapy for patients with severe sepsis. The thing to remember about this is, it was done in the emergency room, so although people are extrapolating this beyond the ER to the ICUs, that simply was not the setting where it was done. You may or may not, depending on where you practice, ever be asked to see somebody in whom you can implement this protocol in the setting where it was actually done. But what they did was, they took patients, everybody got a CVP line, and they randomized them to management within both arms aiming for a CVP of 8-12, aiming for an MAP of 65, and aiming for a urine output of 0.5 mL/kg/hour. But in addition, in one of the arms they actually measured the oxygen saturation out of the CVP line, and they further titrated to get that number over 70%, reflecting adequate tissue perfusion.
I think people commonly misunderstand this study as being about aggressive resuscitation versus less aggressive, but in fact, aggressive resuscitation, according to standard criteria, was done in both arms. The difference was in looking at the venous oxygen saturation, and if it was less than 70% and the hematocrit was less than 30, which again is higher than most people’s transfusion threshold normally, they gave blood. If the hematocrit was over 30, they gave dobutamine. There was quite a bit of dobutamine given in this study.
Results of Rivers study

The results were pretty impressive improvements in a variety of endpoints and a variety of subgroups, looking at 28-day, 60-day, and in-hospital mortality. It’s also notable that what they were preventing was not multiorgan failure, but they were preventing death from cardiovascular collapse. What did they not look at in this study? They did not actually look at renal function, so if you ever wanted to feel like Rodney Dangerfield, now is your time. It would seem like this is the thing that we would want to know - did it actually improve renal function? - and it was not actually reported.
Interestingly, there was another study published in a less-read journal, which actually randomized the more basic part of the Rivers protocol. This was done in Taiwan and is a very interesting study; 224 patients admitted to the ICU with CVP lines where they actually randomized everything. They said one group would get protocolized CVP elevation to 8 to 12, MAP of 65, and a urine output target, and the other group was managed according to clinician discretion. And the interesting thing about this, is that first of all, quite a lot of people had renal dysfunction, both groups going in. They defined renal failure upfront. They noted that fluids and pressors were more rapidly administered in those who were treated according to protocol, and that the mortality was significantly improved in those who got protocolized management. They also noted that there was decreased failure of several organs and decreased multiorgan failure but that protocolization did not improve cardiovascular collapse deaths. So I think the message here, is that our belief that more aggressive management with fluid resuscitation and moving on to vasoactive drugs when indicated, is probably going to result in decreased death from cardiovascular collapse, but also decreased development of organ failure, is somewhat supported by these couple of studies.
ARF Prevention/Therapy: Inotropes

• **“Early” Goal-Directed Therapy**
  - Improved survival in septic shock pts. randomized to E.R.
    resuscitation titrated to normalize \( S_vO_2 \geq 70\% \), using dobutamine, transfusion) vs standard care (CVP >8-12; MAP>65mmHg; UOP >0.5ml/kg/hr)

• **“Late” Goal-Directed Therapy**
  - No difference in mortality or renal function (creatinine, urine output) with either supranormal CO/DO\(_2\) or maintenance of \( S_vO_2 \geq 70\% \) with dobutamine versus control in 762 ICU patients
  - Increased mortality with supranormal oxygen delivery (dobutamine) versus control in 100 ICU patients (54% vs 34% mortality)

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**ARF prevention/therapy**

What is not supported by these very early management studies is the idea that we should apply the same approach to someone who has been in the ICU for a week, because it was tried for many years to do increased oxygen delivery to supranormal levels to truly erase any possibility of oxygen deficit in critically ill patients. In fact they found that in this large study, for instance, there was no difference in renal function in optimizing venous oxygen saturation or cardiac output in a large trial. Of course one of the things that led to the end of this approach was this trial in the medical ICU setting where mortality and cardiovascular events went up when giving a lot of fluid and a lot of dobutamine to critically ill patients with late sepsis.
Pharmacologic Approach to Optimization of Renal Perfusion

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Pharmacologic approach to renal perfusion
We don't actually know if we can extrapolate these early goal-directed therapies to late. Having said that, I will tell you that it seems a commonsense practice to aim for a CVP of 8 to 12, to aim for an MAP of 65, and to aim for that kind of urine output. In looking for evidence of ongoing tissue hypoperfusion, if somebody has got a CVP line in, why not get a central venous gas? If it turns out it's 50% instead of 70% and you are wondering if somebody is still prerenal, I think at least you have still got some evidence of ongoing tissue hypoperfusion and that seems to be a commonsense, but I would say, an unvalidated, approach to reversing acute kidney injury if it's due to a hemodynamic cause. There is also the issue, of course, of what about this mean arterial pressure of 65? I bet if I polled everybody as to what they are titrating pressors to, we would get a lot of different answers, and why don't we try a systolic blood pressure of 90? Anybody order that? Anybody see the nurses doing it anyway? Commonly, people get titrated to something like a systolic pressure everybody is not scared of. People will have very different mean arterial pressures with a systolic pressure of 90, so it's almost certainly not the right answer for everybody, but most people will vary in terms of MAPs of 60 to 80 and where their comfort level is. And of course there is a lack of guidance in the literature, which I'm going to go through with you, as to what exactly we should do here.
Autoregulation of Renal Blood Flow

If you go to your classic physiology textbook, you will note that first of all the human physiology textbook usually has a picture taken from a dog study like this, and it will note that autoregulation works really well to cause vasoconstriction and prevent increased renal blood flow as you raise mean arterial pressure, but that pretty soon after you drop less than an MAP of 90, which is normal, you start to get a drop off of renal perfusion. So where on this curve should we be aiming to optimize renal blood flow?
Perfusion pressure (MAP) target

It's kind of interesting. In animals, when it was looked at, there was some suggestion that there is not an endless gain in titrating up pressors to higher levels and you don't necessarily gain renal blood flow and GFR by doing this. For instance, in this setting, they took animals which were made endotoxemic, and you can see we've got two groups, one of which was actively managed and the other of which was kept unresuscitated. You can see that in both groups after endotoxin, the mean arterial pressure drops. What they did then in the subsequent 2 hours, is they raised the pressure by 10, and then 20 mmHg from the shock level. You will note, that although there was an improvement, and mean arterial pressure obviously in both cases seems to be significant, and although cardiac output got higher, going up 10 points, and higher again, going up 20 points, the portal venous blood flow, the jejunal blood flow, the renal arterial blood flow, and laser Doppler blood flow within the kidney really only improved significantly in going up 10 points, but there was no further gain, particularly in the kidneys in going up 20 points. So was there some kind of signal here that maybe going from less than 60 to over 60 was useful, but going up to 70 or 80 might not be useful? Was there anything from humans to support that?
Shockingly, when you look at the Surviving Sepsis Campaign criteria, which a lot of intensivists use to decide how to manage septic patients, and in fact which are being used to accredit ICUs increasingly as to whether they are doing an adequate job or not, the reference for what MAP to choose to titrate your pressors was this paper from 10 patients where using a variety of tissue perfusion measures, they looked at turning up the pressors from 65 to 75 to 85 mmHg mean arterial pressure. The only urine parameter looked at was urine output. This was found not to increase, and this is the primary data used to say that 65 was the target, and there was no point in turning up the pressors. Obviously that has been somewhat supported by the finding that at least there was a positive outcome with the Rivers goal-directed therapy study, although of course that was not a randomized aspect of the trial.

**MAP effects on renal function**

The only randomized trial looking at perfusion pressure in critically ill patients is this study, which kind of went by unnoticed, I think, in 2005. What they did in this really tiny study, was took patients who had already been resuscitated to an MAP of 65 and randomized 14 in each group to stay at 65 for a subsequent 8 hours or to go up to 85 after a period of stability at 65 to see if there was any gain in, among other things, renal function.
Outcome of MAP effect

What you will note, is that here you’ve got urine output, serum creatinine, and let’s focus on creatinine clearance as the most relevant thing; that comparing first and second data at 4 hours, you will note, that in the group that went up in this period from 65 to 85, there was no significant gain in creatinine clearance or for that matter urine output during this period. Believe it or not, that’s probably the best evidence that 65 is where we need to be and there is no point in going up to 85. Having said that, we all know that there are chronically hypertensive patients who have calcified vessels who have not had an MAP of 65 since before they were born, and that’s not going to be good enough for them, but unfortunately it’s not going to be based on evidence, but rather on clinical management, to decide how high you turn their pressors up to try and aim for an adequate perfusion pressure.
I'll also point out that, internationally, it's very variable as to where people titrate pressors. For instance, in the ANZICS trial, which I think best showed that low-dose dopamine does not effectively treat acute renal failure in ICU patients, the patients who were randomized in the two groups to dopamine versus placebo were looked at at baseline. Two-thirds of them in each group were getting catecholamine pressors to maintain their blood pressures. There was a quite a lot of shock at baseline in these patients. They were all well fluid resuscitated with CVPs of 13 and 14. What is notable, is their pressors were titrated to an average mean arterial pressure of 80 in both groups, which does not reflect, I believe, most United States practice. More European centers go for higher levels too, but as I've said, I don't believe that choosing a target value anywhere over 65 is supported by literature.
### Choice of Vasoactive Drugs

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### Choice of vasoactive drugs

What about the choice of drugs? We've already talked a little about dobutamine as an inotrope. We're going to talk a little bit about norepinephrine versus dopamine, and we're going to talk a little bit about vasopressin.
Norepinephrine vs. dopamine

Norepinephrine versus dopamine is actually the only randomized trial of one catecholamine pressor versus another. What was interesting about this study, is they found in patients with pretty significant shock, that starting with a baseline blood pressure of an MAP in the 50s with treatment with norepinephrine in the randomized study, they could effectively reverse shock, whereas in this study in patients with well-developed shock, dopamine, even at 25 mcg/kg/minute, didn't work. If they took patients who had failed 25 mcg/kg/minute and put them on a small dose of norepinephrine, they could effectively get their blood pressure up. While doing this, of course the SVR went up and the urine output went up when they finally raised perfusion pressure. No change in lactate. The significance of this study is that dopamine, I think, is underappreciated. It's not a direct-acting vasoactive drug. It acts to increase norepinephrine levels in the nerve terminal by effecting reuptake of norepinephrine. If someone has been in shock for a long time they no longer have anything to alter in the nerve terminal and therefore dopamine does not work as a pressor if you have been in shock for a while. So that if you are serious about giving someone a pressor, just get rid of the dopamine and give him either phenylephrine or norepinephrine because they will actually do the job with more certainty. Again, I don't think that's an appreciated thing and, in fact, I think everybody likes dopamine because for those who still believe that dopamine affects renal blood flow favorably at low dose, they can use it for that. They can turn it up as an inotrope. Then they can turn it up higher as a pressor. Well, I'm going to tell you from this that if you think that you are turning it up to be a good pressor, you are probably failing in somebody with significant shock.
Effect of NE in human septic shock
The randomized trials looking at renal effects of norepinephrine in human septic shock. I think you would be surprised if I then rolled out a bunch of randomized trials of Levophed versus other things, and of course I will not. But what they have shown in noncomparative trials, is as opposed to perception that Levophed actually worsens renal blood flow and worsens renal function, of course if it's treating refractory hypotension, more often than not it actually helps renal blood flow, renal perfusion, and renal function. And in fact, in consecutive series when you look at it, usually the urine output and the GFR, when it has being looked at in noncomparative studies, goes up at 24 hours and later.

You may also have seen a lot of interest in vasopressin based on the fact that it was found, that as opposed to CHF patients, patients with septic shock had low vasopressin levels, which seemed inappropriate, since as you have heard, once you get more than about 7% to 10% decrease in mean arterial pressure or extracellular fluid volume, you should actually increase vasopressin from a nonosmotic stimulus. It appears that septic shock patients don't do that. To summarize, I think the reason they don't do it is, they exhaust their posterior pituitary stores of vasopressin. The question is - should you replete that in order to raise their blood pressure?
Norepinephrine vs. vasopressin
There were some very interesting things done. First of all, in a pilot study which was done in Canada before a large randomized trial, they took patients over a short 4-hour period who were all getting norepinephrine drips systemically to maintain their blood pressure at the target range, and in the background they randomized them to add either a blinded norepinephrine drip at a fixed rate or a blinded vasopressin drip. What they showed was, that as you might expect, they required a little bit less norepinephrine and a lot less in the group that got the norepinephrine drip in the background, but a very major sparing effect of norepinephrine in those who got vasopressin.
Effect on urine output
But what was interesting is, actually the urine output went up significantly, even during a 4-hour period getting blinded vasopressin...
Effect on creatinine clearance
...and so did the GFR, in a way that didn't happen with background addition of more norepinephrine, suggesting there might even be some kind of particular renal hemodynamic effect of vasopressin at the same perfusion pressure.
More RCTs

There followed a couple of other small pilot randomized trials. This one, again as you can see, this literature is plagued with 10 versus 13 number studies, but you can see that randomizing vasopressin versus norepinephrine with a baseline mean arterial pressures of 70s-80s, you can see that the pressure really is increased by either one, so is the SVR. Urine output really is not any different, but measured creatinine clearance did seem to actually be higher in at least one time point, significantly so with vasopressin, but qualitatively, really looking quite a bit better in those with vasopressin, again suggesting some potential renal benefit.

20 adults with fluid-resuscitated septic shock randomized to NE or Terlipressin titrated to MAP 65-75 mmHg. Both maintained MAP, Terlipressin with lower CO / oxygen delivery. Equivalent in improving renal function.

Terlipressin versus NE
Another randomized trial done here, again looking at creatinine clearance, didn't show the same thing with terlipressin, which as you heard earlier is more a vasopressin analog but not exactly the same thing.
Vasopressin and septic shock trial

What I think will be very interesting, and this is a paper that you should watch out for during the year, is the Canadians recently completed a very large randomized trial of vasopressin versus norepinephrine in septic shock. And this vast study looked at mortality as a primary endpoint, the bottom line being that, I suppose disappointingly, they found no difference in mortality between the two groups, and this is, as you might imagine, by far the largest randomized trial of any vasoactive drug in critically ill people. They did prespecify that they would look at mortality in those who are on a lot of pressor upfront versus less pressor upfront to finding more or less severe septic shock. It should be noted that they did find lower mortality in those who were less sick to start with in a prespecified subgroup analysis. And in other subanalyses, presented so far only in abstract form, they may have found less progression to severe acute kidney injury than those who had some renal dysfunction at enrollment. There may be some subset outcomes of this and some further trials, but the truth is that overall it did not support superiority of vasopressin over norepinephrine.

Vasopressin And Septic Shock Trial

- 779 patient multicenter RCT of blinded vasopressin 0.03U/min vs. NE, with open-label NE
- Similar baseline characteristics in 2 groups
- No difference in primary endpoint: 28-day mortality (35.4% Vaso vs. 39.3% NE, p=0.27)
- Vaso. decreased open-label NE dose, but not organ dysfunction
- Lower mortality with vaso. in less severe septic shock (NE dose <15µg/minute; pre-specified subgroup analysis)
  - [American Thoracic Society annual congress abstract A596, May2007; personal communication Dr. Keith Walley]
- Vaso. reduced mortality and progression to severe AKI in those with early AKI at enrollment
  - [ATS abstract A596, May2007]
Renovascular resistance: renal vasodilators

Let's just say we accept that we're going to have to raise the CVP to a certain target, maybe 8-12, we're going to have to get the venous saturation to 70%, we're going to aim for an MAP of 65. What about renal vasodilators? Is there anything to support using these? Well, first of all, it's not at all clear that decreased renal blood flow causes acute renal failure and sepsis. It's quite conceivable that no matter what we do hemodynamically, patients will develop cytokine and inflammatory-mediated acute kidney injury, and we're wasting our time titrating all these things if we're trying to prevent renal failure.
RBF in sepsis

But having said that, I should say that probably the best thing you can do to prevent renal failure in a hemodynamic sense is to optimize renal blood flow, and the best thing you can do in that sense, when it was looked at in this large analysis of a variety of experimental models, is to optimize cardiac output. Before we get into looking at renovascular resistance in renal blood flow, what I want you to note here, is that when renal blood flow has been measured in a variety of experimental settings, in those who were found to have decreased renal blood flow, they were always really the animals that had a low cardiac output and a hypodynamic state, whereas it was much more likely that renal blood flow was unchanged or increased in those who were actually well resuscitated and hyperdynamic, and I think that's an important point.
Renovascular resistance in sepsis

In contrast, when renovascular resistance has been looked at in all those same experiments, it's been all over the map. Some of these animals, and this is looking at both mean arterial pressure, which is basically the same across the three conditions, you can see, that with the same mean arterial pressure and different levels of renal blood flow, you can find renovascular resistance essentially all over the map in all kinds of different models.
Increased renovascular resistance
It's not consistent to say that, for instance, somebody with septic shock has increased renovascular resistance like somebody who has cirrhosis and hepatorenal syndrome. I think many of us have felt for years that endothelin, for instance, would be a good target to inhibit to increase renal blood flow in septic shock, and that was supported by some of these experiments, but it may not be the case that it's relevant in human clinical sepsis.
Role of endothelin in endotoxemic ARF

For instance, just to give an example of endothelin as an attractive target, this canine study with endotoxemia looked at direct measurements of GFR from both kidneys, right and left kidneys. During baseline and then during endotoxemia, where after LPS, both kidneys suffered a decrease in GFR, the left kidney got an anti-endothelin antibody infused into the renal artery and you can see that that appeared to prevent the drop in GFR, which didn't happen with the sham antibody.
**Effect of endothelin antagonists**

There have been subsequent animal studies showing that endothelin antagonists can do similar things, probably more endothelin A than B antagonists, but none of this has translated into clinical practice. Of course, what we do know is, that things like dopamine, fenoldopam to a lesser extent, and other nonspecific renal vasodilators, have not yet been proven to decrease the incidence or severity of acute renal failure. I know Dr. Bonventre will go over that more tomorrow. I guess what I would like to point out here, is that if any of this is going to work, it’s going to work here, before you have got the acute renal failure in a prophylactic sense, not when you are developing the acute renal failure, or have moved on to tissue injury, and perhaps even microvascular injury with inflammation and microvascular dysfunction, where a simple systemic vasodilator or renal vasodilator has no chance of doing anything useful. The time when all the trials have been done with these renal vasodilators is when the creatinine has gone up, which is in the timeframes indicated, and in some cases, even several days. In all fairness, in the therapy of acute renal failure, these substances have never been tested at a time when they have any chance of really doing anything.
Synergy and ATN
The last point I was going to make with regard to this, is that of course we have been talking about optimizing renal perfusion, but in fact it’s just as likely that things like endotoxin and nephrotoxins of other kinds synergistically, or perhaps alone, cause the acute kidney injury that we see in patients.
Hemodynamic Management of Severe Sepsis/Septic AKI

- Hemodynamic management of septic shock is aimed to avoid cardiovascular collapse and/or organ dysfunction, including AKI
- Early goal-directed hemodynamic support may improve renal function in addition to outcome in severe sepsis and septic shock
  - Dobutamine is the preferred inotrope; titrated to achieve $S_{CV}O_2 \geq 70\%$
- Limited current literature support the use of vasopressors (norepinephrine, vasopressin, or both) to attain a target MAP of $\geq 65$ mmHg in septic shock patients refractory to fluid resuscitation or inotropic support
  - Routinely targeting MAP $> 65$ mmHg is not supported by literature, but may be required in individual patients
- Renal vasodilators are unproven for AKI prevention or therapy

Hemodynamic management of severe sepsis
Right now I would say, in order to optimize renal perfusion and improve renal function, it's reasonable to aim for the minimal targets of the early goal-directed therapy. The CVP of 8-12, the MAP of 65, and I would say, if you've got a central venous oxygen saturation, a catheter that you can get a blood gas from, measure it and find out if it's very convincingly low, because it gives you something else to resuscitate. And then I would say, that based on what we know in terms of pressors, by all means they should be used if they are needed to maintain an MAP of 65 in someone who's got a decent filling pressure and a decent cardiac output, but renal vasodilators are not supported at this point, and I sincerely doubt that Dr. Bonventre will say otherwise.
Treatment of severe sepsis
In terms of other things to treat severe sepsis, many of you may have seen or treated patients with corticosteroids. What you should know, is that this, again, is an area of evolving literature.
Low-dose steroid treatment
First of all, I think it's worth looking at the original pivotal study. How many of your hospital's intensivists are giving steroids to pressor-dependent septic shock? I don't know if you have looked at the original study. It was done based on the fact that it had been previously shown in small randomized pilot studies, that in those who had pressor-dependent septic shock, giving them steroids decreased their pressor requirement, but they had not done an outcome study. So, here they did an outcome study where they took patients requiring pressors with septic shock. And they randomized them after a baseline period and a test with ACTH stimulation to get hydrocortisone 50 mg IV q.6 h. for seven days plus mineralocorticoid versus placebo and looked at 28-day survival.

Mortality in low-dose steroid treatment

The first thing that should be noted, is that overall there was no significant difference in survival, although they had prespecified that they were going to use in post hoc analysis, the ACTH stimulation results to break down the population further.

Nonresponders versus responders

When looked at in that way, they found that 77% of the subjects had a bump with ACTH of less than or equal to 9, which they predefined as nonresponders to ACTH stimulation, and they showed there that there was an improvement in survival in those who got steroids, corticosteroids and mineralocorticoids, whereas if anything the trend appeared reversed in those who got steroids and basically didn't need them. This was the basis for steroid therapy getting into all the recommendations for treatment of septic shock. Now, what I'm going to tell you to watch out for in the next year here is there is a study being done in Europe, the CORTICUS study, which I have not seen presented but I have been told appears to contradict this and suggests that adrenal insufficiency treatment is not beneficial in terms of outcome in septic shock. What it looks like has become a fairly standard thing may go away again if the results of this are valid. I would say of course that we have to look at the entry criteria and some other aspects but we may have to withdraw this as a standard recommendation.
Activated protein C
What about activated protein C? How many of your hospitals are using this for patients with severe sepsis and organ dysfunction? Probably the answer would have been more a couple of years ago.
Properties of activated protein C
The idea of this is that it treats a few things. It treats the hyperthrombotic state: it’s an anticoagulant, treats the thrombosis and microvascular thrombosis of sepsis. And it also has antiinflammatory effects, effects on neutrophil function, and effects on cytokine production. One attractive thing here, was that all these failed mediator-inhibitor trials in sepsis had always picked one thing to inhibit, and it was very unlikely that we’re going to pick the one thing that works in all sepsis patients at all times, so at least here they had a couple of different mechanisms of action, in a way like steroids, where you might have more chances of hitting the target. They treated patients in randomized trials.
Prowess Study: Inclusion Criteria

- Known or Suspected Infection
- SIRS
  - 3 of 4 (temp, HR, RR/pCO₂, WBC)
- Organ Dysfunction
  - CV: SBP ≤90 / MAP ≤70 mmHg for 1 hr
  - Renal: UOP <0.5ml/kg/hr for 1 hr
  - Resp: PaO₂ / FiO₂ ≤200-250 (solo vs combined)
  - Heme: Platelets <80,000/mm³ or 50% decrease in 3d
  - Acidosis: (unexplained) pH ≤7.3 or base deficit ≥5mmol/L with lactate >1.5 ULN

PROWESS study
This is the PROWESS study, with known or suspected infection, systemic inflammation, and development of end-organ dysfunction. They had to be randomized within 24 hours of the organ dysfunction developing. The development of renal organ dysfunction, which was not common as an entry criteria in here, was a pretty unsophisticated 1 hour of oliguria. And you will note, the more you look at the critical care literature, the poorer the quantification of renal function has been in the trials to date.
Exclusion criteria
What's also interesting though, is the exclusion criteria. In particular, there was a lot of exclusion of people with bleeding risk who in real life ended up getting treated with activated protein C in units all around the country, and renal failure was among the exclusions.
Results: 28-day all-cause mortality

They found an improvement in survival, a 6% absolute reduction in mortality.
Survival curves
Here are the survival curves.
Summary of mortality results

- drotrecogin alfa (activated) significantly reduced mortality in patients with severe sepsis
  - 6.1% absolute reduction
  - 19.4% adjusted relative risk reduction
  - Consistent effect on the relative risk of death across subgroups examined

- Number needed to treat to save one additional life equals 16


Summary of mortality results
They found the number needed to treat was 16 to save one additional life. Although this is an expensive therapy, in many units, in patients deteriorating with end-organ dysfunction with severe sepsis, the practice has been to use the drug.
Results: Safety

- Serious bleeding events
  - Serious bleeding event rate: 3.5% in drotrecogin alfa (activated) group vs. 2.0% in placebo group (p=0.06)
  - Incidence suggests one additional serious bleeding event for every 66 patients treated with drotrecogin alfa (activated)

- No other safety concerns associated with treatment on the basis of:
  - Organ dysfunction
  - Incidence of new infections
  - Hematology and chemistry data
  - Vital signs
  - Incidence of anti-Activated Protein C antibody formation


Safety

Now of course there were some bleeding events in the original study and it trends towards more bleeding in activated protein C, which was not significant but a concerning trend. No other safety concerns emerged.
But what happened, was that subanalysis suggested that perhaps there was more benefit in treating patients with more severe sepsis with APACHE scores over 25 than those less than 25, and naturally a lot of hospitals wanted to limit the use of this very expensive drug to those who would get the most benefit. As a result, they ended up doing a trial of the drug in those with less severity of illness and finding no benefit, and in fact, significantly more bleeding in those who got activated protein C. So this was the first thing that peeled people back from using the drug extensively.
Continued controversy

In addition, there has been some controversy. For instance, it was pointed out in this opinion sent in to *New England Journal* that the Surviving Sepsis Campaign guidelines were flawed in perhaps industry influence, that in fact activated protein C got a higher grade of evidence in the campaign than giving antibiotics for sepsis, which seems illogical except when you consider that there are zero randomized trials of antibiotics to treat septic shock, and I don't think there will be, whereas at least they had one for activated protein C. But somewhat unusually, the drug was approved with 1 pivotal trial, not 2 randomized trials but 1, and the requirement was that they did these followup registries in adults and in children. Interestingly, as the results of those came out, to summarize what has been shown, the bleeding rates have been much higher than they were in the original PROWESS study. Of course these were not randomized trials, so we cannot assess benefits. All we can say is that the number needed to harm is going up, and we don't actually know from a second randomized trial whether there is a true benefit.
Potential utility

Having said that, this is going to be an evolving area, because there are other emerging data suggesting that this drug has beneficial mechanism of action. For instance, in animal experimental models, protein C deficiency is a predictor of developing septic acute renal failure. And giving activated protein C to animals appears to prevent and treat septic acute renal failure. So it will not surprise me if we end up with a randomized trial of this drug to prevent or treat septic acute kidney injury. The trick is going to be figure out how to do it safely without causing excessive bleeding. I think the issue here is going to be in a sense like thrombolytics for coronary syndromes - how do we find the right population and do it safely? But at this point it's still approved. It should be reserved, I would say, to people with APACHE scores over 25 who are definitely deteriorating despite standard therapy.
Mechanical ventilator strategy
What about mechanical ventilation strategy? Again this is an area with a lot of evolving literature and I'm not going to dwell on some of this literature, which shows that acute kidney injury appears to cause acute lung injury because of volume overload.
Pulmonary-renal syndromes
This is all animal data so far. They are probably also wet because of a new kind of acute lung injury.
Renal effects of mechanical ventilation
What I'm going to focus on are the renal effects of mechanical ventilation. Everybody knows that when you intubate somebody and put him on positive pressure ventilation, if they are at all hypovolemic, they are going to get hypotensive and require volume resuscitation, and that's obviously one cause of worsening renal function in that setting. There are other causes. Particularly in patients with very stiff lungs and high intrathoracic pressures, they get back pressure down through the IVC out through the renal vein, which decreases renal perfusion pressure because renal perfusion pressure is the balance of mean arterial pressure against renal vein pressure. If that goes up, you need a higher MAP in the same way you would in someone with abdominal compartment syndrome to get adequate renal perfusion. It's not as simple as just systemic hypotension or clearcut hypovolemia.
ARDSNet trial
But it's also, as I'm going to hope to persuade you, not just a hemodynamic problem that you end up with renal dysfunction in patients getting mechanical ventilation. The ARDSNet trial examined ventilating with smaller tidal volumes. This was a study where the original protocol they did was randomizing to 6 mL/kg of ideal body weight tidal volume versus 12 mL/kg ideal body weight. And it was important to note that ideal body weight in their patients like some of us, is not anything close to their actual body weight so that it was important to do the calculation. But you can see that there was clearcut improved survival and increased liberation from the ventilator with survival in those who got lower tidal volumes.
Tidal volume study issues

As I said, you had to do the predicted body weight calculation. There were some questions raised subsequently about did people really use 12 mL/kg in practice? A lot of people did, but maybe some people used 10 and they needed a 6 versus 10 comparison. Nobody is going to do this trial again to sort that out. Another issue here is when you lower tidal volume, if you raise respiratory rate to a certain level, you cannot go any higher, and ultimately you have to tolerate what is called permissive hypercapnia. One of the issues this raises, is how tolerant are we of permissive hypercapnia and what things might it do? First of all, it has been shown that cardiovascular tolerance of permissive hypercapnia is pretty good in those who have intact catecholamines. You don't want to do this in somebody who's got raised intracranial pressure, because you'll increase intracranial pressure if you tolerate hypercapnia.

ARDSNet Tidal Volume Study Issues

- Predicted Body Weight Calculation (kg)
  - Men: 50 + 0.91 (cm of height – 152.4)
  - Women: 45.5 + 0.91 (cm of height – 152.4)
- Standard of Care comparison?
- Permissive Hypercapnia
  - Cardiovascular effects
  - CNS effects
  - Other effects
  - Buffering issues
Approach to pH management

What I wanted to focus on here just briefly is the area of controversy between intensivists and nephrologists, which is, we don't really like looking at pH values of 7, and sometimes intensivists are very comfortable with that in the sense that they will say permissive hypercapnia is okay, it has been well validated, we're happy with it, and we don't want you to buffer it. What I would point out to them is that this is the guideline from the original ARDSNet tidal volume study. I'm sorry I added this after the major slides, but the point is not to look at the actual protocol they used. The point is that bicarb was permitted per protocol in the original study and that if anybody had a low pH less than 7.3 and in particular if they got less than 7.15 and they didn't respond to increasing the respiratory rate, they were allowed to eventually even go up on their tidal volume and they were also permitted to give them bicarb. So there was nothing in that original successful outcome study to say that it's wrong to buffer patients. In fact when you look back at the original study, the pCO2 values are not very high and the pH values are not very low. I don't believe that there is any contraindication to giving bicarb in this setting.
Kidney-Lung Protective Ventilation?

- ARDSNET Tidal Volume Trial
  - In addition to improved survival and ventilator-free days, low $V_T$ group had more days without circulatory, coagulation, and renal failure (renal. 20±11 vs. 18±11 days, p=0.005)
  - ARDSNet: NEJM 2000;342:1301-08

- Lung-Protective Mechanical Ventilation Strategy
  - Less inflammation in Lung Protective Strategy group
  - Fewer pts. with organ system failure, and markedly fewer with renal failure (p<0.04) at 72 hours in Lung Protective Strategy group

Kidney-lung protective ventilation
What was interesting in a subanalysis of post hoc analysis of this study, is that it appeared like lung-protective ventilation, where lower tidal volumes, less mechanical stretch, and less ventilator-induced lung injury, certainly improved getting off the ventilator, and certainly improved survival. It also decreased the rate of acute renal failure. So what they found was that there were fewer days of renal failure in the original study. In another randomized trial of lung protective ventilation, they found less systemic cytokine production, less inflammation with lung protective ventilation, but also, and I will show you this data, markedly less renal failure in patients who got lung-protective ventilation.
Kidney-protective ventilation
Here is this data from the Canadian study showing an entry versus 72- to 96-hour later period in those who got conventional ventilation versus lung-protective ventilation. Looking at cardiovascular failure, renal failure, and hematologic failure, you can see the interesting one is renal failure, driving all of the overall benefit in decreasing organ failure. For instance, looking at entry versus 72 to 96 hours later, there is a major increase in acute renal failure, defined by creatinine increase in the patients that got conventional ventilation versus lung-protective ventilation in whom this simply does not happen. So it might be that we’re going to decrease the rate of renal failure in the ICUs through mechanical ventilation strategy rather than something we’re doing to try and affect renal blood flow by ourselves.
Pulmonary edemagenesis

The ARDSNet group have now moved on. They tested approaches to fluid management and whether it had benefits in critical illness. This has major implications for nephrologists consulting in the ICU, and I think it's a study you need to be very familiar with. The theory has been that in those with acute lung injury with increased capillary membrane permeability, that lowering hydrostatic pressure in the glomerular capillary will decrease pulmonary edemagenesis, and this has led many units, including our own over the years, to aim for lower filling pressures in those with acute lung injury, ARDS, to try and get them off the ventilator quicker, and presumably prevent things like nosocomial infections, get them out of the ICU, and improve their survival.
Barnes Hospital study
What was this supported by? Well, the best support for many years was, of course, a variety of animal experimental data, but also a human study from Barnes Hospital, where they took a hundred patients and they measured extravascular lung water on all of them using this indicator dilution tool. And they randomized them to be managed by routine according to their CVPs and wedge pressures, or to titrate therapy to actively decrease their extravascular lung water.
Days of mechanical ventilation
They were measured in both groups, but in this group they made a conscious effort to dry them out more than they would have by standard management, and found that there were fewer days of mechanical ventilation in those who got the protocol to get the extra fluid removal...
Days in ICU
...and fewer days in the ICU, but of course it was too small a study to show a mortality benefit.
FACTT trial

It took over 10 years to get a study together in a multicenter trial done by the ARDSNet group, which was the FACTT trial. I have already mentioned to you that this was done by the ARDSNet group, that it had a 2 x 2 design which tested CVP line versus PA catheter, which showed no difference but also tested wet versus dry. And I can tell you, when I saw the design of this a few years ago, knowing that they were going to aim for CVPs less than 4 and wedges less than 8 versus 10-14 and 14-18, I was thinking we were going to see a lot of renal failure, and I'm sure everyone would have expected the same thing. None of the data about ventilator-induced lung injury causing kidney injury had emerged at that point. So there did not seem to be any upside to a nephrologist in having somebody run this by. They completed their study with 1000 patients. They looked at survival, ventilator-free days, etc.

**Outcome of FACTT trial**
Here is what they found. No significant difference in survival, while the bad news there is, that was their primary endpoint.
Main outcome variables

The good news, if you like to be an optimist, is that among their secondary endpoints was ventilator-free survival. They found a significant improvement in patients surviving off the ventilator in those who got dry management as opposed to wet management. This appeared to support the primary hypothesis only if you ignore the fact that the primary endpoint was negative. I think you can tell where I’m going with this!

Unfortunately, they failed the primary endpoint but improved ventilator-free survival. There was a variety of subset findings; more CNS failure in those with a conservative strategy, so maybe drying them out caused more brain injury; who knows, with so many subset analyses? But interestingly, there was not an increase in renal failure, there was not an increase in shock. All of the management was computer protocolized with approaches to fluid, dopamine, diuretics, what have you, according to what is going on with the patients. But there was also no difference in the rate of dialysis, which was measured within the first two months in those in the study. Again, you might have said, with patients running that dry, that you would have expected more dialysis. So in fairness, that did not happen.
Dry versus wet trends
Because I think you are going to hear a lot of discussion about vigorously drying out patients with acute lung injury if you have not already heard it, I think it's important to know a few more details about this study. First of all, their definition of renal failure as an endpoint was a creatinine going over 2. As you know, you can have an awful lot of renal failure and not get your creatinine over 2. So that's a pretty blunt instrument in terms of detecting kidney injury. So, their renal failure-free days were not different based on this definition. It should be noted as well that there was a trend towards higher creatinines in the dry group. It was 1000 patients, with a P value of 0.06, so a few more hundred patients, and who knows, there might have been more renal failure. Furthermore, there was more hypokalemia in the dry group, and there were higher bicarbs and significantly higher BUNs. So I believe there was more renal dysfunction. It just did not happen to meet the criteria. Of course if we had the kind of biomarkers that are being developed now to look at acute kidney injury, we might have seen all kinds of signs of occult acute kidney injury. And why do I keep bringing this up? Am I so reluctant to accept the fact that they successfully got people off the ventilator that I cannot accept the results of the study? Maybe. However, I think you have to be conscious about the fact that despite the fact they got people off the ventilator quicker, their survival was not improved and maybe that's because some bad things happened. Maybe they hurt their brains, maybe they hurt their kidneys, and part of this is, I guess, in view of what is happening in development of drugs in other areas other than acute kidney injury. There is talk that the FDA will approve ventilator-free days as an endpoint for studies of treatment of acute lung injury, and I think that in case of the nephrology, we have been held to having to improve mortality overall, and it might be that dialysis-free survival is at least more achievable than that and hopefully will get support of that idea from studies like this, if this is generalized into practice.

So what I would say here is - we know their BUN is up, we know their creatinine is up, we're asked to see the patient - you will want to give the patient fluid, you are
able to say the study was negative, and you are honestly correct in that. If their aim is to get them off the ventilator, they will probably be unperturbed, and they will still refuse to give them fluid, but the truth is that the evidence is actually on your side at this point.

Summary: Lung-Kidney Interactions

- Mechanical ventilation effects renal function through hemodynamic, neurohormonal, and inflammatory mechanisms
- Use of lower tidal volumes in ALI/ARDS improves renal function and survival
- Fluid conservative management improves respiratory failure-free survival, without severe adverse renal effects
- The optimal approach to pH management with permissive hypercapnia in ALI is unclear
- AKI adversely affects pulmonary function

Lung-kidney interactions

Having said that, looking at lung-kidney interactions, there are a variety of mechanisms - we need not go into all of them - but certainly hemodynamic as well as some neurohormonal and inflammatory mechanisms whereby ventilation hurts kidney function. Lower tidal volume is a very convincingly positive study. It appears to decrease kidney injury as well. You can certainly improve ventilator-free survival with fluid conservative management. It’s not clear whether renal injury is increased by that or not, but at least severe renal injury with dialysis does not seem to be increased by that approach. In terms of pH management, in patients getting permissive hypercapnia, I did mention that bicarb is okay for someone with a pH certainly less than 7.15 according to their own protocol from the ARDSNet study. What I did not point out is that there is experimental evidence in animals that low pH actually decreases the severity of acute lung injury. As that literature evolves, there may also be resistance to correcting it because it might actually increase the severity of lung injury. That has not been shown by human study to-date.
Severe Sepsis Therapy: Conclusions

- In addition to adequate therapy of infection, the use of early goal-directed hemodynamic support and a number of other adjunctive measures are now proven to improve outcome in severe sepsis and septic shock.
- Adrenal function testing ± corticosteroid therapy should be performed in all patients requiring pressors.
- Activated protein C helps patients with severe sepsis and evolving organ dysfunction, but not sepsis of lesser severity.
- Supportive care should also include appropriate mechanical ventilation, tight glucose control, fluid balance management, aggressive RRT dosing, and prevention of nosocomial infection.

Sepsis therapy conclusions
That will be an area of ongoing discussion, and then you are going to increasingly see, and I would not be surprised if Dr. Bonventre showed some of it, evidence that acute kidney injury, actually in reverse, causes and exacerbates acute lung injury. In terms of sepsis, in addition to aggressive therapy of infection, I would still suggest renal function testing, and that until the CORTICUS trial comes out and we get to assess it, particularly in patients who are failing pressors, you may still consider corticosteroid therapy. Activated protein C, I think has its place for more severely ill patients, but you have to err on the side of avoiding it, I believe, in people with increased bleeding risk because it appears like more and more evidence is suggesting that that's a problem. And of course what I have not covered here is the overlap area which is renal replacement therapy which will come up extensively in the other two lectures, but it looks we have time for a lot of questions, so if you want to bring up that aspect or anything else let's go ahead with the questions.

Thanks for your attention.

References


therapy in the treatment of severe sepsis and septic shock. 


Patrick Murray, MD
Dr. Patrick Murray is an attending nephrologist and Director of the Acute Dialysis Unit at the University of Chicago Hospitals, Chicago, Illinois. He attended medical school at University College Dublin, Ireland. He completed a residency in Internal Medicine at Hennepin County Medical Center in Minneapolis, Minnesota. He then completed fellowships in Nephrology, Critical Care Medicine, and Clinical Pharmacology at the University of Chicago Hospitals. He is an Associate Professor, and Director of the Hospitals' Nephrology fellowship training Program. He conducts clinical research in the prevention, detection, and management of acute renal failure in the ICU. He is Editor of a forthcoming textbook entitled "Intensive Care in Nephrology", which will be published in 2005, and is co-edited by Professors Hugh Brady and Jesse Hall.