Katy Grainger

Hi, my name is Katy Grainger and four years ago this month I lost seven of my fingertips and both of my lower legs to sepsis. One thing that's interesting about my story is that the reason that it got so severe with me, I actually ended up in septic shock, is because I did not know the signs and symptoms. So when I tell my story I can't stop myself from kind of highlighting where I made some mistakes. So in September of 2018 I was living in Hawaii with my husband, we were new empty nesters, and I had just gone to visit my kids in California for a week and my husband had taken that opportunity to go on a fishing trip to very remote Idaho. So I went down to California, hung out with my kids, and then it was time to return back to Hawaii. I got on an airplane, flew home, and when I got to the airport, this is when I remember noticing that I had this bump on my finger and it was oozing. It was kind of pink and it had clear fluid coming out of it. So it looked different than anything I'd seen before.

So I was on my way home, my house is actually an hour from the airport, it's also an hour from the hospital which is gonna be relevant later on. So I did decide to go by the emergency clinic. When I got there I showed them the cut and they agreed that it did look infected and looked like it could possibly be MRSA. They took a little swab of it and said basically they'd call me in a few days if anything grew out of it. So they gave me a prescription for antibiotics and they said to start taking them if it got worse over the weekend. At the emergency clinic when they checked my vital signs everything was great. So they didn't have any indication that I had success at this point and I really didn't, I just had an infection.

So on Saturday morning I woke up, I hopped in the shower, it was warm there in Hawaii, I was kind of warm but I never was registering a fever. So I didn't think there was anything wrong. I did notice that the infection on my finger was getting a little worse so I went ahead and took an antibiotic. Well soon thereafter I threw up but I just thought it was because I had taken an antibiotic on an empty stomach and I wrote it off. But I ended up sleeping through the afternoon and sleeping through the evening and sometime in the middle of the night I got up and I probably went into the bathroom which is two steps up from my bedroom and what we think may have happened is that I maybe stood up quickly and low blood pressure in my body caused me to pass out. But what the result was is that I broke my left foot, I sprained my right ankle, and I had just a mark on my knee where I had fallen on the floor. So this is a sign for me of mental decline because instead of calling for help like a normal person would, I crawled back in bed.

So the next morning was Sunday and I woke up at sunrise, like at the crack of dawn, I could hear the roosters outside, it was still dark. And I don't really remember much. I do know that I texted my friend and I said to my friend, 'Can you take me to the hospital?' She asked if we could go to the emergency clinic and I said no, I have never been so sick. So my friend took this seriously as one should and she came right down to my house, let herself in, and she found me nearly unresponsive in my bed. We tried to stand up and that's when we realized that my feet hurt. We found out later that it was the break in the one foot. And then I also could have had some nerve pain from somethings you're gonna hear about in a second. But it was about an hour drive and about 15 minutes out I started crying in the backseat saying, 'Are we there yet? Are we close? My hands and feet are on fire.' So she went ahead and called the hospital and let them know that we were coming in.

When we got to the hospital they met us with a gurney, they got me out of the car, loaded me onto it. They took me right into the emergency room and they did the things that they should do, took my vital signs. So it turns out that my blood pressure at that point was 50/30 which is extremely low. And it's funny because I read my chart and they said I was conversant and pleasant. And I'm like well that's my go to. I mean I was faking conversant and pleasant. I also had an increased heart rate and I had low blood oxygen so they immediately put an oxygen cannula in my nose just to let me breathe oxygen. Later in the day the oxygen levels got worse and I actually had a mask forcing air into my lungs.

So what was happening is that my organs began failing. I stopped urinating, so that was a sign that my kidneys were failing. And it was becoming really clear that I was at the higher levels of sepsis called septic shock. The whole thing with my hands and fingers are on fire is showing that my circulation at my extremities was very, very bad and my fingers began turning purple and so did my toes although I didn't see them at the beginning. I ended up having a condition later that they diagnosed called disseminated intravascular coagulation. So if this had not happened in the hospital I would have run out of platelets. So at that point in time I was on an outer island in Hawaii, we lived on the island of Kauai. Anyone in Hawaii, if you get sick on an outer island and you get very sick and you need an ICU or you need severe help, they will transport you by air ambulance over to Oahu which is where Honolulu is.

So on Monday morning a bed became available at the hospital at Queen's Hospital, it was decided that they would fly me over to Honolulu. So they ended up giving me medication to put me in a drug induced coma, they intubated me, and they sent me over to Oahu. When I got there my husband had actually, thank goodness, had landed on Oahu about an hour before I did. So he was able to meet me at the hospital, so now I have my family with me. When they came out they told him that I was not stable and started asking questions like does she have a will and what are her desires if we need to resuscitate? But they did say that he should call our children who again were in California and have them come because they weren't sure I was gonna make it.

So my family was by my side for five days as I sat in the ICU, or as I laid in the ICU. And they were praying over me and watching my hands and feet turned more and more purple, up to my wrists and up to my ankles. And it became clear I think to them during that week that I was going to lose at least my fingers and toes and likely more than that. On my daughter's 23rd birthday, my oldest daughter's 23rd birthday which was five days later, I woke up. And when that happened I saw my husband in front of me and he got right into my face to just let me know he was there and that everything was going to be okay. I was extremely confused but one thing that happened is I saw my fingers go in front of my face and seven of my fingertips were black. My thumbs, the tips of my thumbs were black. It looked like I was going to lose all of my fingers and I was absolutely terrified. I didn't know what had happened. Last I remembered I was being cheerful talking to people in the hospital and then I'm waking up and I'm realizing that I can see these clearly dead fingers, I realized I'm going to lose these fingers.

So we spent three weeks at the hospital doing hyperbaric chamber every day and doing nitroglycerin cream on my hands and feet three times a day. It was extremely painful but we were able to save my hands. Right now I have my hands and most of my fingers up to those seven tips that were black. My thumbs are fine, I have them 100%. I'm really fortunate that that's what my outcome was. At the time I was really trying hard to save my feet and I was having, as you can imagine, a very hard time admitting that we might not be able to. After three weeks I finally looked at my husband and said I understand that we can't save my feet and I just want to move on to whatever the next steps are. After a couple of months I got the amputations, I did recovery at home.

I got my prosthetic legs right around Christmas time. This happened in the middle of September initially. And I was able to stand on them immediately but it was painful. So I just built up my tolerance to walking around in them just slowly. I stayed in my wheelchair a lot of the time. And anyways I started getting better and I started realizing I could get my life back. I went and visited my daughter, she went to Rome for study abroad and my husband and my best friend arranged for me to go as well. So I got to go visit her like I had always dreamed of doing and since then I'm living a really full life. A year later I was invited onto the Board of Directors of Sepsis Alliance and now I share my story to spread awareness.

TPWKY	(This Podcast Will Kill You intro theme)

Erin Welsh	Katy, thank you so, so much for being willing to share your story and taking the time to tell your story. It's terrifying.
Erin Allmann Updyke	It's terrifying. And thank you too for all of the work that you do raising awareness and sharing your story not just with us but with so many people.
Erin Welsh	Yeah. It's amazing.
Erin Allmann Updyke	Yeah.
Erin Welsh	Well. Hi, I'm Erin Welsh.
Erin Allmann Updyke	And I'm Erin Allmann Updyke.
Erin Welsh	And this is This Podcast Will Kill You.
Erin Allmann Updyke	It's a big old episode today.
Erin Welsh	It really, really is. It's a big one.
Erin Allmann Updyke	It is.
Erin Welsh	We're covering sepsis.
Erin Allmann Updyke	Sepsis.
Erin Welsh	Which is not like a one size fits all definition.
Erin Allmann Updyke	Oh, I can't wait. I have a whole paragraph called 'Definition? Never had that before.'
Erin Welsh	Yeah, it's a big one but it's also tremendously important and I don't think I realized before we started digging into this just how prevalent and scary and kind of still there are a lot of open questions.
Erin Allmann Updyke	Oh Erin, I feel like all I have are open questions when it comes to sepsis. So yeah, it's going to be probably heavy at times but it's going to be I think a really good episode and really interesting.
Erin Welsh	Yeah.
Erin Allmann Updyke	Yeah.
Erin Welsh	For sure. Well should we start off this episode like we do every other episode?
Erin Allmann Updyke	With a quarantini time?
Erin Welsh	With a quarantini time. What are we drinking this week?
Erin Allmann Updyke	We're drinking Let Us Spray. I love it so much.

Erin Welsh	I do too. So this is a reference to Joseph Lister and his carbolic acid spray which will make up a big part of the history section later on in the episode. And I just want to give credit to Doug for giving us the idea to use this as our quarantini title. It is one my favorites.
Erin Allmann Updyke	It's really fantastic. Thanks Doug. Erin, what is in Let Us Spray?
Erin Welsh	Let Us Spray is a delicious little blended cocktail with cherries and ice cream and lime juice and maybe some whipped cream on top and some vodka if you want to toss that in there, up to you.
Erin Allmann Updyke	Just casually.
Erin Welsh	Yeah. And we will post the full recipe for Let Us Spray, both the quarantini as well as the non alcoholic placeborita on our website thispodcastwillkillyou.com as well as on all of our social media channels.
Erin Allmann Updyke	Any other business, Erin?
Erin Welsh	I don't think so. I think we should just get started because I have a feeling this is going to be a big episode.
Erin Allmann Updyke	It's going to be great. We will take a short break and then get into it.
TPWKY	(transition theme)
Erin Allmann Updyke	I think probably moreso than any condition or infection or disease that we've covered on this podcast, sepsis is something where the actual definitions of sepsis have changed so many times even in recent years. So I can't wait to compare how we identify sepsis today to how we understood it historically.
Erin Welsh	I don't know if I'm going to be going into any of that.
Erin Allmann Updyke	But I bet we'll learn a lot about it.
Erin Welsh	Perhaps.
Erin Allmann Updyke	So what I wanted to start off with was just what are the definitions of sepsis because there's kind of a lot floating out there. So here's one from a 2019 paper I will quote. Quote: "Sepsis is a medical emergency that describes the body's systemic immunological response to an infectious process that can lead to end stage organ dysfunction and death." Another that comes from The Third International Consensus Definitions Task Force and is kind of the consensus definition known as Sepsis-3, the third iteration of this, is a bit shorter. "Sepsis is a life threatening organ dysfunction caused by a dysregulated host response to infection."
Erin Welsh	Okay, that makes sense.

Erin Allmann Updyke	Right? It does. And they go further to then identify a specific subset of sepsis and that is septic shock which is a subset of sepsis in which underlying circulatory, cellular, and metabolic abnormalities are severe enough to substantially increase the risk of mortality. Basically very, very serious and severe. But even that definition of sepsis and septic shock, even though they are considered consensus definitions, have changed a lot over time. And even today that definition doesn't necessarily precisely apply in pediatric populations which happen to be at particular risk for sepsis as we'll talk about later. So because the definitions of sepsis have changed over time, so has the diagnosis or the criteria that are used to diagnose it. And I think that that's kind of the best way to think about sepsis. It is a process but it's also a diagnosis that's used to kind of triage and determine management if somebody ends up in a hospital setting. Does that make sense?
Erin Welsh	Yeah. And it's interesting that the criteria have changed so much. First of all, why is that? And second of all, how has that affected, this may be way jumping the gun, but how has that affected more current numbers or being able to compare throughout even the past few decades how our ability to control sepsis has changed?
Erin Allmann Updyke	Yeah. That is all very important and really good questions. Basically it's made it difficult. So our numbers on sepsis, as we'll talk about later in this episode, aren't great. Especially our understanding of the rates of sepsis and control of sepsis in low and middle income countries. And you do have to kind of take into consideration every study that's done, what were the criteria that were used to identify sepsis vs to rule people out for sepsis or whatever?
Erin Welsh	Yeah.
Erin Allmann Updyke	But basically the definitions have changed in part because of our understanding of sepsis and what the underlying causes are as well as how we identify it in an emergency setting, for example. And the truth is there are a whole host of what are often called screening tools that are used to kind of identify in ideally a highly sensitive way what people might either have sepsis or be at high risk for sepsis. One of these screening tools is called SIRS. It stands for Systemic Inflammatory Response Syndrome. And these criteria are like an increased or decreased temperature, an increased heart rate, an increased respiratory rate, an increased white blood cell count or a severely decreased white blood cell count, things like that. So having two of those criteria and a known or suspected source of an infection would in a lot of cases rule people in, so make us think this person has sepsis, we're going to call them sepsis until proven otherwise.
	There are a lot of other criteria. There's the SOFA which stands for Sequential Organ Failure Assessment which is mostly based on a list of laboratory values or respiratory status values to kind of try and determine and triage the degree of organ damage. So getting a certain score on that screening tool plus having a known or suspected infection would then meet criteria for sepsis. But there are also a lot of others. There's one called NEWS, there's one called MEWS. There's likely different versions in different countries that I don't even know about.
Erin Welsh	And so what determines which screening tool you use? Is it just where you are or what hospital you work in?
Erin Allmann Updyke	Exactly that, where you are and what hospital you work in.
Erin Welsh	Yikes.

Erin Allmann Updyke	So I can tell you we use SIRS very often. SIRS has a number of detractors and it definitely is not a perfect screening tool, no screening tool is perfect. But it is used very often as one of these possible screening tools. Now there is an organization, I think you would call an organization, it's called the Surviving Sepsis Campaign and it's an international organization that really tries to go through all of the data that we have on sepsis and outcomes of sepsis and come up with a consensus set of guidelines on how to identify, diagnose, and manage sepsis in the hospital and ICU setting. And so they have a set of guidelines and things where they say this screening tool is not the best and this one is okay and etc, etc.
Erin Welsh	I have a question.
Erin Allmann Updyke	Okay.
Erin Welsh	So about the number of all these screening tools, does that mean that sepsis is difficult to recognize because the symptoms are varied or is it because there are a lot of other things that can look like sepsis and the treatment is different?
Erin Allmann Updyke	Yes and both.
Erin Welsh	Okay.
Erin Allmann Updyke	So yeah, it's hard to tell you exactly what the symptoms of sepsis are because they're incredibly non specific. So in general, according to our definition, people have some sign of an infection. This could be a pneumonia which tends to be at least in hospital settings the most common identified cause of sepsis but certainly not the only one. It could be a urinary infection, it could be cellulitis, it could be a tiny cut on your finger. So that could be the initial infection. But then in terms of the other symptoms that you might see, people may or may not have a fever, they may or may not have an elevated heart rate as a physiologic response to this infection, they may or may not have difficulty breathing or if you put an oxygen meter on them have hypoxia, decrease in their oxygen status.
	They may or may not already have progressed to the point of hypotension, so decreased blood pressure which is when you're getting into the point of having septic shock and we'll get more into that. They may or may not if you look at laboratory numbers have changes in their liver or their kidney function or their platelets. They may or may not have altered mental status or even be unconscious. But it's a really mixed bag and any and all of those signs and symptoms could point to sepsis as a cause but there are plenty of people that come into a hospital setting or are already in a hospital setting that have many of those signs or symptoms but do not have sepsis.
Erin Welsh	What do they have?
Erin Allmann Updyke	They could have any number of other things. They could have cancer, they could have just meningitis but not have sepsis. They can have anything.
Erin Welsh	Okay, question. Do the symptoms that somebody has vary more based on who that person is, maybe their age, maybe their history, etc, or the infection that has caused or led to sepsis?

Erin Allmann Updyke	That's a good question. It's a hard one to answer. I would say there are things that we tend to look out for in certain age groups as an indicator that might make us more worried about sepsis vs might make us more worried about something else in a different age group. For example, altered mental status is one especially in the elderly that you might not see as much in younger people with sepsis, though you certainly can. And then same thing for if they have respiratory symptoms, you might think that they have a predominantly respiratory infection that's the cause of sepsis. But sepsis can lead to respiratory symptoms even if the infection is elsewhere in the body. So it's a whole mess.
Erin Welsh	I think this might be even more complicated than whatever one has 'It's Complicated' in the title of the episode.
Erin Allmann Updyke	Right. I know and the truth is all we've done is try to define what sepsis is.
Erin Welsh	Right.
Erin Allmann Updyke	That's all we've tried to do.
Erin Welsh	Yeah.
Erin Allmann Updyke	And it's really difficult. But I think that at its core that short and sweet Sepsis-3 definition, organ dysfunction as a result of a combination of both an overwhelming infection or at least I like to think of it as an overwhelming infection and a dysregulated immune response to that infection. I think that those things can tell us a lot about the process underlying sepsis even in the face of the fact that specific criteria to call someone septic might be different at one hospital vs another. So at its core sepsis requires first an infection. And this like I said can be an infection of literally any body area, cellulitis, pneumonia. And often we think I think classically of sepsis as resulting from a bacterial infection.
	And some papers even go so far as to say like gram-positive cocci, things like Staph and Strep which are common all over our skin are the most common cause of sepsis-related mortality. Some statistics say that. And then they'll go on to say that gram-negative rods like E. coli which commonly cause UTIs are the second most common cause of sepsis-related mortality. But the thing is that sepsis can be caused by any bacterial infection, true, but also fungal infections and even viral infections. And so then it gets even more complicated because you have culture negative sepsis where you're maybe treating like it's a bacterial infection but with no evidence of bacteria growing from any body source.
Erin Welsh	Okay, a couple of questions here.
Erin Allmann Updyke	I know. I can see your face being like why?
Erin Welsh	No, my brain is like wait, you have to stop because I have too many questions for you to go on. Number one is what's the breakdown of bacterial vs viral vs fungal and how much of that is just sort of in the culture negative ones? Like we don't know what the sepsis was caused by because we're not detecting any bacteria but could it still be bacteria?
Erin Allmann Updyke	Yeah. We don't know, we don't have great numbers on that in general.
Erin Welsh	Okay.

Erin Allmann Updyke	40% of sepsis cases can come back as culture negative. And we have some stats on like the most common sites of infection, so 64% of cases at least that we have numbers on are starting in the lung, 20% in the abdomen, 15% in the bloodstream, 15% in the genitourinary tract. But that still doesn't tell us that it's necessarily a bacterial infection, though those most commonly are going to be ones that we've identified as bacterial infections. Fungal infections tend to be probably the least common but the most severe. If you have an overwhelming fungal infection, you're likely very, very, very sick. And viral infections are probably way underdiagnosed. And this is where it gets both more interesting and so much more complicated because if you think, as an easily recognizable example, of COVID-19.
Erin Welsh	Yeah.
Erin Allmann Updyke	The vast majority of people hospitalized, that ended up in the hospital or the ICU for COVID-19, would meet many if not all of the common criteria that we would use to diagnose sepsis. They're probably tachycardic, their heart rate is through the roof. They probably have an oxygen requirement, they may or may not have a low blood pressure. They probably have some evidence of further organ damage like kidney or liver damage and certainly they have an overwhelming infection in their lungs and a huge amount of inflammatory response in those lungs causing acute respiratory distress. So people with COVID-19 would by many definitions or many sets of screening protocols meet quote "sepsis criteria".
	And yet it's probably only either in an emergency like triage setting or in the very early days of the COVID pandemic that most of those people were actually classified as having sepsis. Because now on their discharge paperwork they would be called having COVID-19. Right? Because we know that that damage is being wrought by SARS-CoV-2 and our dysregulated immune response to that virus. But instead of calling it sepsis necessarily, we call it COVID-19. And so some people might argue you should still call that sepsis and some people might argue you shouldn't. So yeah.
Erin Welsh	I wonder if sepsis in the future is going to be one of those things where people are going to look back and go, 'You used this catch-all term to describe something.' Like fever.
Erin Allmann Updyke	Right.
Erin Welsh	We look at fever back in the 1700s.
Erin Allmann Updyke	Yeah, yeah. It's really interesting. It's a good question. Because a similar thing happens in pediatric populations and that's part of why sometimes the definition for sepsis in pediatric populations might be a little different than adult populations because there are so many respiratory viral infections especially that children get hospitalized for all the time that might meet some sepsis criteria but aren't generally classified as sepsis because we know that it's bronchiolitis or whatever.
Erin Welsh	Okay, so sepsis is a diagnosis of exclusion?
Erin Allmann Updyke	Kind of the opposite. Sepsis is a diagnosis of inclusion. Sepsis is this is a person who is very sick and we might not know exactly what they have yet but they're very, very sick and they look like they're going to get sicker.
Erin Welsh	Okay.
Erin Allmann Updyke	So we treat it like sepsis until we can determine if it's something else.

Erin Welsh	Okay. So using the example of COVID-19, could somebody have severe COVID-19 and then could somebody else have COVID-19 sepsis or is sepsis not really directly ever tied to a specific infection and then how does that impact treatment?
Erin Allmann Updyke	Yeah, great questions. Yes, people can have an infection like COVID and still have sepsis. People can also seem to have sepsis initially but then recover very quickly. And so then you kind of get into did we just treat the sepsis very well at the beginning and so now they didn't move on to septic shock, etc? So then I don't know, there's just so much still up in the air when it comes to how you fully draw that line of is this sepsis or is this not sepsis? And I think a lot of that is place dependent. But the treatment does vary at least according to kind of what we have for now as consensus guidelines when it comes to early identification and treatment of sepsis. So let's get into a little bit more of why do we even have to have this definition of sepsis and what does that mean? What's going on in our bodies? And then we can talk about how we then treat that because of what's happening. Does that make sense?
Erin Welsh	Yeah.
Erin Allmann Updyke	So while sepsis requires an infection as we talked about it is not purely an infection. Not every person with a UTI or pneumonia or COVID is going to go on to have sepsis. Sepsis is what happens when an infection gets so severe that our immune system reacts to it in such a way as to cause severe damage to one or more of our other organs as a result. And if this process continues unchecked, our immune system and the infection can continue to spiral which will lead to septic shock and eventually death.
Erin Welsh	And when you say severe infection does that mean bacterial load, viral load? What does that mean?
Erin Allmann Updyke	Yeah. I don't have an answer as to what that means because we don't have an answer as to why did that person with a UTI go on to be septic and this person with a UTI didn't.
Erin Welsh	Two people could have the same viremia and one person could develop sepsis and the other one may not?
Erin Allmann Updyke	Right. Because what did their immune system do initially to try and counteract that?
Erin Welsh	Okay.
Erin Allmann Updyke	Did they suppress it well enough or did they not?
Erin Welsh	Okay.
Erin Allmann Updyke	Right? Did they overreact? Did they underreact? Did they do a little bit of both? Yeah.
Erin Welsh	Okay.
Erin Allmann Updyke	I can tell that's not a satisfying answer.
Erin Welsh	It's fine.

Erin Allmann Updyke

To talk about septic shock for a quick minute because it's a really important part of sepsis, we've talked about this concept of shock on the podcast a number of times. Shock is essentially when you aren't getting enough perfusion, you're not getting enough blood flow and therefore oxygen to your organs. So shock is another one of these catch-all definitions where you can have shock from a whole bunch of different processes but shock is characterized specifically by hypotension, low, low blood pressure. And so that means that your organs like your kidneys, your liver or your brain, your heart, they're not getting enough blood and oxygen to function so they begin to shut down. And that is what leads to death in sepsis. It's multi organ failure as a result of septic shock. So what exactly is our immune system doing in response to an infection that eventually results in this all the way down the line? No more blood getting to our organs, not enough oxygen getting to our organs.

Erin Welsh

Yeah.

Erin Allmann Updyke

So unsurprisingly we don't fully understand this mechanism at all, especially when we get into the nitty gritty details of it. But what we do know is that sepsis is characterized by a very dysregulated response to infection. So what we see is both proinflammatory and anti-inflammatory mediators being released at the same time which we used to think that it was like pro-inflammatory first and then you went through a phase and then your immune system shut it down and then went into this anti-inflammatory phase. But it turns out that this is all happening at the same time. It's like our immune system is just on overdrive, just trying to do anything that it can.

Erin Welsh

It's just kitchen sinking it.

Erin Allmann Updyke

Exactly. One of the major pathways that we think is involved in this severe pro and anti-inflammatory response is this specific group of receptors known as PAMPs, Pathogen-Associated Molecular Patterns. And these are kind of specific antigens, specific sugars or proteins that are present commonly on pathogens like bacteria on their surface that all tend to fall into certain patterns. There's one as an example called LPS or lipopolysaccharide, that's one type of PAMP. There's a lot of different variations that many different types of bacteria might have but they all have these patterns that lets our immune system recognize that's one of those LPS'. And then we have these receptors, toll-like receptors that recognize these. And this hugely stimulates our innate immune response which tends to be our first pathway of protection against pathogens.

So these receptors see these PAMPs and they send out alerts and activate both of these systems at the same time. They're stimulating systems to increase the amount of inflammation and at the same time they're stimulating systems that are anti-inflammatory as well. And then those systems, those pro-inflammatory actors are releasing cytokines, they're telling the whole rest of our immune system get in gear, bring all the leukocytes, tell everyone this is war! I don't like that analogy but it's really good. And it basically sends our immune system into overdrive. All of this inflammatory process causes vasodilation, so it opens up our blood vessels really wide so that the inflammatory stuff can get to where it's trying to go.

And this inflammation also causes damage to the blood vessel walls and inflammatory changes to the layers of our blood vessel walls so that things can squeeze out and get into tissues to help heal them. But what this ends up leading to is leaky blood vessels, edema of the tissues, fluid getting out to where it doesn't belong. And so if that fluid gets into something like our lungs, then that can lead to severe difficulty breathing called acute respiratory distress syndrome because of fluid filling up your lungs that's supposed to be in your blood vessels. This also leads to a decrease in permeability of your blood-brain barrier, so then infections can spread to the brain where they maybe couldn't before. And that's all just the inflammatory pathways that are happening during sepsis.

Erin Welsh	Okay, so I have a question about this.
Erin Allmann Updyke	Okay.
Erin Welsh	This seems like a very maladaptive response to infection. And so is this process, does this whole cascade of inflammatory and anti-inflammatory response, whatever, is that good in moderation? And is it only in this specific context or certain context that it can be triggered to this massive overdrive that leads to oh, that was too much buddy, okay, that's it?
Erin Allmann Updyke	I think that's kind of a fundamental question that we still have about the underlying path of physiology of sepsis and who's at risk for sepsis and why.
Erin Welsh	That's my other question.
Erin Allmann Updyke	Yeah.
Erin Welsh	So I know that sepsis can happen to anyone but why does it seem to happen in the highest rates in elderly people and in young children?
Erin Allmann Updyke	So one of the biggest risk factors for sepsis and I think this is really interesting in the context of a dysregulated immune response, rather than just thinking of it as like an overactive immune response, is that one of the biggest risk factors for sepsis is immunosuppression, whether that's primary immunosuppression or poorly controlled HIV or very elderly, the immune system is just not what it used to be or the very, very young, like infants and neonates don't have a fully on boarded immune system yet. Those are the groups that are at highest risk for sepsis.
Erin Welsh	That makes sense. And so because when you were talking about that inflammatory cascade and just this overwhelming response, it was reminding me of the 1918 flu and the cytokine storm. But that's a different thing or is it the same thing?
Erin Allmann Updyke	Well that's the thing, right, that's the same thing that we think happens in COVID.
Erin Welsh	Yeah.
Erin Allmann Updyke	So is it a different thing or is it actually the same thing? That's what's happening in sepsis, right. We maybe have a better understanding of the process in very limited disease settings, right. We understand that okay, maybe it was these particular cytokines in the 1918 pandemic. Maybe it is these particular processes in something like HLH or other kind of immune-driven disorders. But sepsis because it's a catch-all, because it's any overwhelming infection that our body is responding to in a dysregulated fashion that's causing this unregulated inflammation, is it just one process or is it each case of sepsis is a slightly different process? And is that part of what's making it so difficult to study and to understand?
Erin Welsh	Whoa, yeah.
Erin Allmann Updyke	Whoa.
Erin Welsh	Whoa.

Erin Allmann Updyke	And I'm not even done because there's more. The second consequence of sepsis besides all of that inflammation is that all of that inflammation has an interaction with our hemostatic pathways in addition to those inflammatory pathways. So this will be a call back to our hemophilia episode. So all of this inflammation and these inflammatory changes end up causing damage to our endothelial cells, those cells that line our blood vessels. And we talked in detail in our hemophilia episode about when our blood vessels get damaged, they release something called tissue factor and tissue factor is one of the first things that stimulates our coagulation cascade.
	Coagulation is the process of being able to clot our blood so that we don't bleed out every time that our skin gets cut or a vessel gets cut. So this coagulation cascade, this process is going to first recruit platelets to come in and plug the holes of that damaged blood vessel. And then tissue factor is going to start the process of activating this whole entire cascade that I'm not going to go back through but it's factors 7, 8, 9, 5, 4, 10, etc. And this whole process ends up getting activated in again a dysregulated way when it comes to sepsis. So what you can end up seeing in a very mild form is just thrombocytopenia which is a drop in platelets because those are the first things that come in to plug a hole when we have a hole in our tissues. But that's mild.
	If this process continues out of control, it will progress to what's called DIC or Disseminated Intravascular Coagulation which is basically when this coagulation cascade is underway inside of our blood vessels and ends up forming these little microthrombi, little tiny little clots in our vessels as a result of this coagulation cascade. And these thrombi not only can block off blood vessels by accident, so now you're not getting blood flow to say your fingertips or a part of your brain, and at the same time because our body, whenever we make a clot we eventually need to break it down. So when we're forming a whole bunch of clots inside our blood vessels, our body is breaking them down at the same time, we end up using up all of these coagulation factors. We end up using up all of our platelets to the point where now we can't clot at all, so you can end up hemorrhaging.
Erin Welsh	Oh my.
Erin Allmann Updyke	And that is DIC.
Erin Welsh	Okay.
Erin Allmann Updyke	Yeah.
Erin Welsh	And this is happening right alongside or is there any sort of-
Erin Allmann Updyke	Yep.
Erin Welsh	Okay, there's no sequence to the inflammation or not a hard and fast rule.
Erin Allmann Updyke	Yeah, exactly.
Erin Welsh	Okay.

Erin Allmann Updyke	There's not a hard and fast rule and there's not clear sequences. We used to think that there were, we used to think first there's this overwhelming pro-inflammatory response and then our immune system gets suppressed and then the coagulation cascade gets involved. We used to think it was more stepwise but it's not. If you think of it more as a dysregulation, it's that everyone is trying to do something at the same time but there is no communicators, there's no leaders saying this is too much, this is too little, we need to work together. It's like everyone's just a free for all.
Erin Welsh	Okay.
Erin Allmann Updyke	That's at least the way that my brain has tried to understand it.
Erin Welsh	Yeah, yeah, yeah. That makes sense.
Erin Allmann Updyke	Yeah. And then of course there's also a fair amount of immunosuppression that's happening because of these anti inflammatory things that are going on. And it tends to be that T cell lines and in some cases B cell lines, more of our specific adaptive immune response seems to be suppressed although aspects of our more non specific or innate immune responses can also be suppressed. But the problem with this is that it can end up leaving one more susceptible to another infection, a superinfection, right?
Erin Welsh	Oh my gosh.
Erin Allmann Updyke	Yeah.
Erin Welsh	This is a mess.
Erin Allmann Updyke	It is.
Erin Welsh	And there is no hard and fast rule to anything.
Erin Allmann Updyke	You've summed it up. Sepsis. This is a mess.
Erin Welsh	Wow.
Erin Allmann Updyke	The major consequences of course I think I've said are organ failure, septic shock, and death. So this is something that can very quickly progress to a very, very serious emergency situation. So that's why a lot of the definitions of sepsis kind of try to include that in the definition.
Erin Welsh	What is the timeline of that? When you say very quickly, what could that be?
Erin Allmann Updyke	I mean it depends on the infection.
Erin Welsh	Okay, so it could be a matter of hours to days but not not a longer drawn out process than that?

Erin Allmann Updyke	Probably not because once your immune system starts, once you truly have sepsis, this process is just going to continue unchecked unless you're being managed. So let me finally try and answer some of your questions from before on how do we actually treat this. And there are a few I think pretty important principles when it comes to management. I will link to the Surviving Sepsis Guidelines from 2021, those are at least as far as I saw the most recent guidelines. But I will also say and I'll talk about this more later in the episode, these are imperfect and they are in a lot of cases based, they say it outright, this is not my words, they're based on pretty poor quality of data because we just don't have good enough data when it comes to sepsis.
	But there are a few kind of big important things. And the first is just identifying people, especially those that are at high risk for septic shock. And so that means using these various criteria to identify people who have sepsis even if it's early on. The other thing that it means is identifying as quickly as you can the source of infection and if possible getting cultures to be able to verify if this is a bacterial infection, what bacterium it is or if it's a fungus, what fungus it is. It's also possible to do viral testing in some places, in some areas. But identifying the source of infection and then controlling that source if possible.
	So if there's an abscess, it needs to be drained. If there's a necrotizing skin infection, it has to be debrided. If it's an infection from an infected line like a catheter of some kind, being removed. Finding where the bacteria is seeding from or the infection is seeding from and trying to remove it. And in the vast majority of cases starting broad spectrum antibiotics especially if you don't know what is causing this. And then one of the kind of most well supported things that tend to happen when someone is identified as having sepsis is fluid resuscitation. Because it can so quickly progress to septic shock and hypotension, resuscitating with fluids, so putting in an IV and getting fluids is one of the most well studied, has really good data to support that it improves outcomes and mortality.
Erin Welsh	Question about endotoxins.
Erin Allmann Updyke	Yeah.
Erin Welsh	What role do they play?
Erin Allmann Updyke	Great question. So endotoxins are often things like that LPS that I talked about, these can be things that are pathogen-associated molecular proteins that our body is recognizing. So that's one of the main pathways that we've identified that's a likely contributor to the initial development of sepsis.
Erin Welsh	That's one of the triggers.
Erin Allmann Updyke	Exactly.
Erin Welsh	Okay.
Erin Allmann Updyke	If we're talking generally about a bacterium.
Erin Welsh	Right, right. So with treatment, what are the mortality rates?
Erin Allmann Updyke	They really, really vary place to place and case to case. From some data from maybe about 10 years ago in Europe mortality rates from sepsis tended to be about 40% vs about 28% in the US which is massive.

Erin Welsh	Well it's also interesting too because like you brought up earlier what goes on the sheet in terms of diagnosis can also very much affect the mortality rates.
Erin Allmann Updyke	Exactly, right.
Erin Welsh	Yeah.
Erin Allmann Updyke	And in some of those cases if they use statistical methods to adjust for things like how severe was the disease, then those differences where it seems like why is sepsis so much more deadly in Europe than the US? If you actually look at disease severity and sepsis mortality then there actually wasn't a difference. So it does I think in part come back to how broad this definition is and how it can vary place to place and over time.
Erin Welsh	Yeah. Very, very many variables.
Erin Allmann Updyke	Don't you love it?
Erin Welsh	It's interesting, fascinating, scary.
Erin Allmann Updyke	Yeah. So Erin, has it always been with us? I presume yes.
Erin Welsh	I do too. I'm not going to talk that much about that aspect of it but I'll talk about some other ones.
Erin Allmann Updyke	Can't wait.
Erin Welsh	And I'll get started right after this break.
TPWKY	(transition theme)
Erin Welsh	The story of sepsis. How do you tell the history of a condition with such varied symptoms, with such varied causes, with virtually any viral, bacterial, or fungal infection able to lead to its development like you talked about? A condition whose definition and name itself has undergone substantial revision over the past 100 years and one which we still seem to be struggling to effectively treat or even understand. Obviously there are many different ways you could go about it. Talk about a particular bacterial cause or the evolution of treatment strategies or how our understanding and definition of sepsis has changed throughout time. Or maybe you could talk about a big moment in sepsis history, a period when humanity's collective view of the world and how it worked underwent a tremendous and lifesaving shift, even if somewhat reluctantly.
Erin Allmann Updyke	Okay.
Erin Welsh	And that's my pick for today.
Erin Allmann Updyke	Love it.
Erin Welsh	That's what I'm gonna do. Because how could I pass up an opportunity to talk about Joseph Lister and the sanitation revolution?

Erin Allmann Updyke	We simply cannot.
Erin Welsh	We cannot. Of course Lister and his carbolic acid only make up a small part of the overall history of sepsis but I wanted to primarily focus on his work today because I think it gives us a fascinating insight into the early days of germ theory and how we got from germ theory as a ridiculed idea to germ theory as fact and from germ theory as theory, to germ theory in practice. And Joseph Lister is really at the heart of so much of that. And I want to mention at the top that most of the info about Lister and those early days of surgery and germ theory I got from the fantastic book 'The Butchering Art' by Lindsey Fitzharris.
Erin Allmann Updyke	Very great book.
Erin Welsh	It's truly such a great popular science book that is unputdownable, I highly recommend it to fill in more color and more context and more amazing quotes about the early days of the horrific days of surgery to this story. Listeners of the podcast and Erin, you've heard me talk so very much about this time period but we are covering new ground here and I honestly think it's one of the most interesting stories yet. But first let's take a step back to get our bearings with sepsis. Probably could go without saying but humans and sepsis go way back and our recognition of the disease also goes way back, to about 2700 years ago when it was first used in a medical context in Homer's poems in the verb form 'sepo' meaning 'I rot'.
	Later around 400 BCE the word sepsis was introduced in the Hippocratic texts meaning quote "the decomposition of animal or vegetable or organic matter." And this word or variations of it were used extensively in Greek and Roman literature, not just in medical text, but also classic literature and philosophical writings where it likely held symbolic meaning. Over the next hundreds of years it remained in some use but it seems difficult to say whether that was in the medical sense or in a symbolic sense and in either case it's unlikely that the sepsis referred to in most historical texts pre 19th century would always fit the definition that we use today.
Erin Allmann Updyke	Right.
Erin Welsh	The modern use of sepsis more or less can be traced back to sometime in the early 19th century, depending on the language, also depending on the definition. This is why I didn't want to go into the changing definitions of sepsis.
Erin Allmann Updyke	Yeah.
Erin Welsh	It just gets really messy really fast. And when it was introduced in the early 19th century it meant putrefaction, often accompanied with the rotting of the body or parts of the body after a wound. And it's really no surprise that it was around this time that sepsis came into more and more frequent use as well as other words that were related to sepsis like septicemia or pyaemia because much of the world was undergoing some pretty drastic changes in terms of urbanization, industrialization and population growth. And these changes could also be seen in the medical field, namely in the form of hospitals. I talked a bit about the enormous increase in hospitals during this time in the puerperal fever episode.
Erin Allmann Updyke	Yes.

Erin Welsh	Go and listen to it. But in case you need a refresher and you don't feel like it, I'm going to set the stage again here. The late 18th century and early 19th century saw a tremendous growth in hospitals in Europe and in the US mainly as a feature of the cities that were constantly and rapidly growing thanks to industrialization. In contrast with rural areas where doctors would often travel house to house to care for patients, hospitals began to be popular in cities where physicians could just stay put and wait for their many patients to come to them. They could work with other physicians and exchange knowledge and they could use the people seeking care, many of whom were in lower economic classes, as a teaching opportunity.
	Prior to the early 1800s, essentially the only requirement for being a surgeon was just calling yourself one. But with the growth in hospitals also came tighter, though still loose by today's standards, regulations for education and training for surgeons. And would be surgeons had to spend a certain amount of time, say six months or so, learning in hospitals, listening to lectures, performing autopsies, or training directly on patients. Hospitals were proving to be a tremendous opportunity for the growth and spread of medical knowledge as well as the growth and spread of pathogenic microbes. Because these were still the days before germ theory when it was held that the dirtier the surgeon's hands or the stiffer their coat with dried pus and blood, the more respected they were.
Erin Allmann Updyke	It's so yucky.
Erin Welsh	It's horrible to think about.
Erin Allmann Updyke	Yeah.
Erin Welsh	The prevailing notion of what caused disease was still miasma, foul air that contaminated the body and led to infections.
Erin Allmann Updyke	How does your coat not be full of foul air?
Erin Welsh	Did it stink? It had to have. That's what's baffling.
Erin Allmann Updyke	Yeah, it had to have. Yeah.
Erin Welsh	I don't know. But yeah, these blood and pus encrusted surgical instruments or soiled bed linens, these weren't viewed as dirty or needing cleaning. It was the bad air in the post surgical ward that caused the incredibly high mortality rates observed. After all the sight of pus, called laudable pus, in a wound or surgical site was thought to indicate that the body was healing, it wasn't something to be worried about. In the first few decades of the 19th century, mortality rates from surgery were as high as you can imagine. But the overall number of surgeries performed was actually fairly low and that was largely due to the lack of anesthesia.
	Prior to the introduction of ether in the 1840s, if you had to have surgery of some kind you either had to take your chances with laughing gas which could either kill you or not affect you at all or bite the bullet or more accurately the leather strap. The horror of surgeries made many people reluctant to have them unless in cases of dire need and even made many surgeons reluctant to perform them or at the very least encourage them to cut as quickly as they could.

	When ether was first used in 1842 by Crawford Long outside of Athens, Georgia, it was the beginning of a revolution that would transform surgery from a terrifying last resort where a surgeon had to get in and out as quickly as they could into a viable option and a burgeoning field of study. With ether a surgeon still had to be fast but they at least had a little more breathing room to make sure they were suturing the right arteries or whatever together. As the miracle of ether became more widely known across the world, the number of surgeries performed climbed up and up and up. With ether one enormous barrier to surgeries had been toppled but the other one, a big one, still remained. Infection. And infections post surgery loomed bigger and bigger as ether became more widely used since remember we're still in the days before germ theory.
Erin Allmann Updyke	Right. Oof.
Erin Welsh	This is the surgical world that Joseph Lister entered into at the age of 17 in 1844. Lister was born and raised a Quaker which meant a simple childhood, no sport, no theater, no frills. Life in general was not about the pursuit of pleasure but about service and honor of god. Fortunately for little Joseph Lister and the rest of the world, science was considered a worthy pastime and he had the tools to explore the natural world at his disposal, thanks to his father. Although Lister's father had started his career in the family biz as a wine merchant, over time he became fascinated with the world of microscopes, especially in improving their capabilities through fiddling with this lens or adjusting that angle.
	Lister's father's improvements to microscopes earned him great renown and Lister's childhood home was full of the instruments as well as specimens and books of natural history. Given this upbringing, it's hardly surprising that at the age of 14 Lister decided he wanted to better understand life by becoming a surgeon which was not welcome news to his family. At the time surgeons were not a well respected bunch. They were seen not so much as educated professionals but more as crude technicians. To just give you an idea of this, consider that a hospital's chief bug catcher who was responsible for removing lice from mattresses was paid more than the hospital surgeons.
Erin Allmann Updyke	Whoa.
Erin Welsh	Yeah.
Erin Allmann Updyke	I mean that does sound like a difficult job.
Erin Welsh	It sounds like a horrific job, yeah. None of this deterred Lister though. And so in 1844 at age 17 he enrolled in University College London, bringing with him of course one of his father's microscopes. He didn't start right away with medical classes however, his father realized that if he couldn't dissuade Lister from pursuing surgery, he could at least require that he complete an art degree first which was effectively a liberal arts degree with courses in history, math, literature, and science.
Erin Allmann Updyke	I love that.
Erin Welsh	This was definitely not a requirement or the norm for surgeons in training but Lister later attributed his ability to make the important connections he did across disease, sanitation, and germ theory to this well rounded education. The other not required or not normal thing that Lister did was bring his microscope. At the time microscopes had been around for quite a while, over 200 years.
Erin Allmann Updyke	Wow.

Erin Welsh	I know!
Erin Allmann Updyke	I just always forget how early the microscope really came about.
Erin Welsh	It's fascinating.
Erin Allmann Updyke	Yeah, it's really impressive.
Erin Welsh	But even though these microscopes had been around for that long of a time, they weren't yet seen as integral to medicine. Instead they were considered a distraction, a waste of time, or even a threat to the medical community since they promised answers that physicians could not provide with the naked eye. Yeah. But slowly the tides were turning as scientists jotted down observations about how some diseases acted on different tissue types, rather than on just the entire body or whole organs as had been thought. It would still take some time though before the value of microscopes in diagnosis and other aspects of medicine was made clear. And so Lister certainly was unusual in owning one and maybe even more unusual was that he used it.
	As a senior medical student Lister was appointed to be a dresser for John Eric Erichsen who was the senior surgeon at University College Hospital. Part of Lister's duties included standing by with a box of supplies to dress wounds during surgery or to change the bandages in post surgical care. In 1852, during one of these routine bandage changes, he unraveled the cloth on a patient's seeping, rotting wound and was met with a horrific odor. It was the dreaded hospital gangrene. In the days pre germ theory, gangrene was one of the big four exceedingly common hospital infections that caused the most death and disease, with the other three being erysipelas, septicemia, and pyaemia which is the development of pus-filled abscesses. No one knew precisely why hospitals in particular seemed to be so susceptible to these conditions but they certainly were. You may remember some of the stats about puerperal fever in the countryside compared to hospitals from the puerperal fever episode. And here I'm going to do the same thing but with amputations.
Erin Allmann Updyke	Oh dear.
Erin Welsh	Yeah. For instance, in one year in the countryside 23 double amputations were performed and 7 died, which still seems like a lot.
Erin Allmann Updyke	Definitely still a lot.
Erin Welsh	Until you compare with the Royal Infirmary of Edinburgh for that same period. 11 double amputations, 10 of whom died.
Erin Allmann Updyke	Wow.
Erin Welsh	And it wasn't just those seeking care at hospitals that were at risk. Many physicians, surgeons, medical students, and surgical assistants were just the tiniest scalpel slice away from introducing one of these deadly infections into their own bodies. At one hospital, St. Bartholomew's Hospital, over the period from 1843-1859, 41 medical students died after developing fatal infections.
Erin Allmann Updyke	Oh my gosh.

Erin Welsh	And of course I can't not mention the 300% mortality rate surgery where the quote "fastest knife in the West End", Dr. Robert Liston, was cutting so quickly that he sliced off his assistant's fingers and then slashed a spectator's coat. The patient and the assistant died of infection of course while the spectator died of shock. Or so the story goes.
Erin Allmann Updyke	Whoa.
Erin Welsh	Yeah. That possibly true, possibly made up dramatic story aside, the high mortality rate at hospitals and in the cities themselves had come to be expected. Industrial accidents, lack of access to clean water or nutritious foods, crowd diseases, even if you managed to avoid cholera from the contaminated Broad Street pump or tuberculosis from your overcrowded building or arsenic from your wallpaper, you could just as easily die from septicemia after having the gash on your hand you got at the factory stitched up at the hospital. Deadly infections haunted every hospital wing and once one appeared, there was not really anything doctors could do to slow its spread. Within a matter of days the gangrene that Lister observed in that one patient had swept the entire surgical wards and Lister was put in charge of wound care. This involved him scraping off the dead, decaying tissue from the wounds and then applying mercury pernitrate which is both caustic and toxic, an excruciatingly painful process that thankfully was done while the patient was under anesthesia.
	Lister, observant as always, noticed that the wounds that had been very carefully cleaned and that had received this caustic treatment healed surprisingly well. What was it about this process that prevented the gangrene from getting worse? Maybe the answer wasn't in the air as many of Lister's contemporaries thought but in the wound itself. He took some of the pus that he had scraped from patients' wounds and made slides to check out under the microscope. Later he wrote about what he saw. Quote: "I examined microscopically the slough from one of the sores and I made a sketch of some bodies of pretty uniform size which I imagined might be the materies morbi [morbid substances]. The idea that it was probably of parasitic nature was at that early period already present in my mind." Endquote.
Erin Allmann Updyke	And this is pre germ theory.
Erin Welsh	This is pre germ theory but I believe that that was a reflection later on in his life.
Erin Allmann Updyke	Okay, okay.
Erin Welsh	But in any case the seed of a revolutionary idea was planted. But it would take several more years to fully form.
Erin Allmann Updyke	Okay.
Erin Welsh	As Lister neared the end of his medical training he was given awards and accolades and recognition of his exceptional abilities and achievements. But while his professors could see great promise in him, he wasn't so sure. He couldn't decide whether he wanted to go into medicine or surgery, ao one of his professors recommended he spend some time in Edinburgh with clinical surgeon James Syme. What was supposed to be a month long stay turned into years as Syme became not only Lister's respected mentor but eventually father-in-law. In Scotland he fell back in love with surgery and dove back into the topic that had first grabbed his attention in his surgical training, inflammation in wounds. He spent his free time examining more pus and tissue samples under the scope and jotting down any patterns he saw. When did inflammation appear? When did a fever develop? Was fever a good thing or a bad thing? What about inflammation? Did sepsis always come after inflammation or only some of the time?

	He could only get so far with the dead and dying tissue he was looking at so he turned to other living animals to take a closer look. A colony of frogs that he kept at his house. He would injure their webs in various ways using heat or chemicals and then look at what happened to their blood vessels. What these experiments told Lister was that inflammation was a normal part of the healing process and sepsis didn't necessarily follow. He was getting closer. In 1859, 6 years after he moved to Edinburgh to work with Syme, Lister, who was then 32, applied for and was given a prominent surgery professorship at the University of Glasgow. Although at the time the academic atmosphere at Glasgow was conservative, where Edinburgh was daring, traditional while Edinburgh leaned progressive, new hires like Lister were injecting a bit of freshness into the university which attracted more and more medical students. Students who loved their new professor for his riveting lectures, focus on clarity, and modern thinking.
	Alongside his appointment at the university, Lister was also given a position at the city's hospital which he viewed as essential for connecting theory and practice, demonstrating the procedures that he had lectured about in class. Even though the surgical ward that Lister was assigned to was basically newly constructed, it was already filthy. All the classic infections haunted the wards, the graveyard was constantly overflowing, and there was practically nowhere to wash your hands or instruments or bed linens. Even the surgical tools that were used were ornately carved which meant that they were impossible to clean if the surgeon actually attempted to clean it at all.
Erin Allmann Updyke	Ugh.
Erin Welsh	Yeah.
Erin Allmann Updyke	I know we've talked on this podcast about trying to separate what we know now from what we knew back then but I can't get this one. You know?
Erin Welsh	I know.
Erin Allmann Updyke	I can't get there. A pus-filled knife? How are you not going to wash that?
Erin Welsh	Because pus was good. It was laudable.
Erin Allmann Updyke	Actual dirt and blood? Come on!
Erin Welsh	I know, I know. It's very horrible but interesting to think about. Yeah. Lister's house surgeon, get a load of this, said quote: "When almost every wound was foul with separation, it seemed natural at the time to postpone the complete cleansing of hands and instruments until the program of dressings and probings had been finished." Basically what point is there to clean something that's just going to get dirty again?
Erin Allmann Updyke	Yeah. All right, okay.
Erin Welsh	With this attitude, is it any wonder that mortality rates post surgery were sky high? Surgeons weren't being willfully malicious, they simply didn't know any better. But it was still a tragedy to those dying of infection and their loved ones who had to sit by helplessly as well as to the surgeons who would take great care in treating people only to watch them die of infection a few days later. Lister felt this very keenly and as a result he became very invested in trying to prevent these post surgery deaths, starting with cleanliness. The concept of cleanliness has not remained constant throughout history.

Erin Allmann Updyke	Ooh, is that a whole other episode?
Erin Welsh	Yeah, I think it could be. Nowadays we may think of a clean hospital room as one that has been sprayed and wiped down with antiseptic, freshly mopped, fresh linens, a paper on the bed, sterilized instruments, and so on. In Lister's day a clean room was one that had been recently swept and the windows opened. That was basically it.
Erin Allmann Updyke	That was it.
Erin Welsh	Was fresh air. Yeah.
Erin Allmann Updyke	Okay, fresh air.
Erin Welsh	Granted new ideas were continually being proposed, such as cleanliness and cold water, which held that surgical instruments should be cleaned with water that had been boiled and then allowed to cool. And the idea behind this was that cold water was supposed to prevent the heat that caused fever and inflammation.
Erin Allmann Updyke	Why boil it and then cool it?
Erin Welsh	Great question. I don't know. And of course Ignaz Semmelweis went further than just washing instruments in cold water, he also famously advocated for better hand washing and instrument washing using a chloride solution. But as we know, he was ridiculed and his ideas did not become widely known until after his death. So Lister didn't hear about him until much later on. Instead Lister tried out the cleanliness and cold water approach and became increasingly disappointed at the results or lack thereof. It didn't seem to do anything. He expressed his frustration to his students, saying quote: "It is a common observation that when some injury is received without the skin being broken, the patient invariably recovers and that without any severe illness. On the other hand, trouble of the gravest kind is always apt to follow even in trivial injuries when a wound of the skin is present. How is this? The man who is able to explain this problem will gain undying fame?" I know. Endquote.
	As 1864 drew to a close, Lister was still deep in his depression over the seemingly inevitable death of his patients when a colleague brought some new articles to his attention. Research involving fermentation and putrefaction authored by none other than Louis Pasteur. In these articles Pasteur noted that microscopic rod-shaped organisms were found in spoiled wine and he believed that they were responsible for the spoilage. But he also looked beyond wine, proposing that these tiny germs were also responsible for certain diseases in humans and other animals. Pasteur's ideas were met with quite a bit of resistance and ridicule from the medical and scientific community but Lister found them exciting and felt hopeful that the answers he had long been looking for might be found in these articles. To Lister this concept of germ theory explained why disease appeared after surgery and how it could be spread from one person to the next all the way down the ward.
	He wasn't entirely right in his conclusions, believing that it was microbes carried in the air rather than on instruments for instance, but he was on the right track enough to try out some infection control strategies, namely by attacking these germs after their introduction into the wound. On this he also turned to Pasteur who had demonstrated that these germs could be killed by any number of different things. Heat or filtration couldn't really be put to practical use for Lister so he turned towards finding an antiseptic that would kill germs on contact. Again this was not an entirely new notion. Antiseptics had been used by surgeons for years to irrigate wounds but two main things prevented them from being recognized as incredibly powerful sepsis prevention tools.

	The first was that surgeons typically waited to use the antiseptic on a wound until it was obviously infected, at which point there was little the antiseptic could do because the infection was likely systemic. And second was that the antiseptics themselves often caused substantial damage to the surrounding skin, allowing for further infection. Because of this the jury was still out on the value of antiseptics and medicine. Lister wondered if there was more to the story of antiseptics though, so he decided to test different ones out to see which were the most effective in preventing infection. Instead of waiting for the bus to be freely flowing and the surrounding skin hot and tight and red with inflammation, he applied the antiseptics prophylactically and waited to see which one did the best. After going through a few that didn't show much promise, he reached for the carbolic acid aka phenol, remembering that he had heard carbolic acid was sometimes used at sewage works to counteract the smell of rotting liquid waste.
Erin Allmann Updyke	Ew.
Erin Welsh	Yeah. He thought if it can cover up those horrific smells, maybe it'll kill whatever is putrefying these wounds. And I feel like that was also Semmelweis' train of thought but yeah. Carbolic acid didn't work that great on the first two people he tried it out on but the third time was the charm. In august of 1865, 11 year old James Greenlees was brought to Lister's hospital three hours after his leg had been crushed under a cart, tibia cracked and jutting through his skin. Yeah. The wound was already of course filthy from the road and from the journey to the hospital but Lister knew that amputation which was probably safest in terms of infection would forever change this young boy's life.
	And so he wanted to see what he could do. He put the boy under chloroform and went to work cleaning out the wound as best he could with dilute carbolic acid and getting the bone reset. And he continued to take meticulous care of the wound over the next days and weeks, carefully cleaning it with carbolic acid and putting some olive oil on as a soother and checking for signs of infection. Six weeks and two days after James Greenlees had been carried into the hospital with his horrifically broken leg, he walked out on his own.
Erin Allmann Updyke	Wow.
Erin Welsh	Yeah. Lister felt that he finally held the key to the hospital infection problem. He continued to try out his carbolic acid technique on other people with compound fractures with a success rate of 80% and then moved on to other injuries before he finally felt ready to publish. On March 16, 1867, two years after he first began experimenting with carbolic acid, Lister published the first part of a five part article in The Lancet describing his findings. Quote: "On a new method of treating compound fracture, abscess, etc, with observations on the conditions of separation." This was not only groundbreaking in its support for germ theory but his articles also provided step by step instructions to prevent postoperative infections. The Glasgow Royal Infirmary where Lister worked went from being among the deadliest to the cleanest with the lowest mortality rates.
Erin Allmann Updyke	Wow.
Erin Welsh	Lister wrote, quote: "I now perform an operation for the removal of a tumor, etc, with a totally different feeling from what I used to have. In fact surgery is becoming a different thing altogether." Endquote.
Erin Allmann Updyke	Wow.

Erin Welsh	It's hard to imagine what a tremendous relief and how much hope that would have inspired I guess.
Erin Allmann Updyke	Right.
Erin Welsh	Like finally this isn't a death sentence.
Erin Allmann Updyke	Yeah.
Erin Welsh	Yeah.
Erin Allmann Updyke	Especially to have like dedicated your whole life to something and then finally feel like you can do it and not only have horrific outcomes.
Erin Welsh	Yeah, right.
Erin Allmann Updyke	Yeah, I can't even imagine.
Erin Welsh	Yeah. And I have some numbers to back up just how incredible this was. So 16 of the 35 people that had undergone amputations between 1864-1866 before carbolic acid, 16 of those 35 had died, while that number dropped down to only 6 of 40 between 1867-1868 after carbolic acid.
Erin Allmann Updyke	Wow.
Erin Welsh	Yeah, it's amazing. And I do just want to point out because I realize I'm talking mostly about Lister and antiseptic technique in the history of sepsis and a lot of these post surgery deaths were due to wound sepsis basically that was caused by an infection that they had gotten from the surgery, not something they came into the hospital with.
Erin Allmann Updyke	Right.
Erin Welsh	Yeah. As you might expect, Lister's articles weren't immediately accepted with open arms by the medical and surgical community.
Erin Allmann Updyke	Shock of all shocks.
Erin Welsh	Shocking, shocking. Though he did seem to have more supporters than someone like Semmelweis. His old mentor Syme was on his side, as were many of Lister's students and Pasteur himself, whom he became close pen pals with. But there was quite a bit of resistance and even ridicule in response to his ideas of antisepsis, most notably from the famous surgeon James Y. Simpson who had first introduced the use of chloroform as anesthesia and was a big proponent of acupressure for sepsis prevention, which didn't work. Simpson seemed to have a personal vendetta against Lister. Maybe he was frustrated that no one seemed to like acupressure, maybe he felt protective of his own fame and was jealous of Lister. But there did seem to be a variety of reasons that Simpson and others were so quick to dismiss Lister's ideas. To some it seemed like the newest version of 'put this mysterious ointment on it and hope for the best'. To others it was a passing fad. Some believed Lister to be overstating his results and others dismissed it out of hand due to its reliance on germ theory which had by no means been widely accepted yet.

	But perhaps one of the biggest reasons for resisting Lister's ideas was that if he was right, that meant that these surgeons had been inadvertently causing the deaths of so many of the people that they were supposed to have been helping. Lister fought the disappointment he felt from all this criticism by focusing his efforts on improving surgery in other ways, such as changing the material that the ligatures were made of to catgut which could be absorbed by the body and reduce the risk of infection. He also concentrated on teaching, realizing that well if he couldn't convince older generations of doctors of his methods, then he could train the new ones. Over the next few years, years in which so many people continued to die because their surgeons refused to test out Lister's techniques, Lister kept at it, touring across the US to give talks where some hospitals like Mass General for example had actually banned Lister's techniques.
Erin Allmann Updyke	Wow.
Erin Welsh	And then later they were the first hospital to make it hospital policy to practice.
Erin Allmann Updyke	Wow.
Erin Welsh	And also continuing to publish his results. I hate that this is a lesson in publish, publish, publish but whatever. It all paid off. The medical community grew to accept Lister's carbolic acid practices in preventing post surgical infection. And the enormous contribution he made to the field of not just surgery but all of medicine was recognized in his lifetime, unlike so many of the other people that we talk about on this podcast.
Erin Allmann Updyke	Yeah.
Erin Welsh	Lister spent the rest of his life showered in awards, accolades, honorary degrees, and was even given the dubious honor of having a hygiene product created in his name.
Erin Allmann Updyke	Listerine?
Erin Welsh	Listerine.
Erin Allmann Updyke	Oh my gosh! I don't know if I ever put those two together. Listerine has been around that long?
Erin Welsh	It was developed by someone who who saw his talk, one of Lister's talks in the US, and then later the rights to advertise it were sold and the person who bought them advertised it as a dandruff treatment, a cure for gonorrhea, a floor cleaner, and of course oral antiseptic. And that's how it has remained. And it wasn't just Listerine that Lister inspired. Lister's antiseptic techniques kicked off a craze for antiseptic products and inspired someone named Robert Wood Johnson who had also seen Lister speak to join up with his brothers to start a company manufacturing sterile surgical dressings and sutures. They named it Johnson & Johnson.
Erin Allmann Updyke	How interesting.
Erin Welsh	Yeah.
Erin Allmann Updyke	Wow.

Erin Welsh	But mouthwash aside, Lister's two biggest legacies are that he provided an effective means to prevent one of the biggest causes of surgical deaths which absolutely changed the practice of surgery forever and medicine, period. And also that he demonstrated germ theory in action which greatly helped it to become accepted or at least more closely examined. With the widespread adoption of Lister's antiseptic practices, hospital sepsis cases dropped tremendously over the next decades. Researchers learned more about the underlying pathophysiology of sepsis, such as the role of endotoxins and the immune system response, and they discovered new ways to diagnose and treat the condition. In the 155 years since Lister published his article, we've come so far and learned so much about sepsis. But as we can gather from the biology section, we have still so very far to go. And I really hope I haven't disappointed anyone too very much by skipping over most of the recent history of sepsis and the changing definitions but I figured, Erin, that you could at least bring us up to speed with sepsis today.
Erin Allmann Updyke	Oh I can't wait to right after this break.
TPWKY	(transition theme)
Erin Allmann Updyke	Sepsis today. Erin, it's a bit of a mess. So in the US in recent years there are nearly a million sepsis cases admitted to hospitals each year. Just in the US.
Erin Welsh	A million.
Erin Allmann Updyke	Yeah. And the numbers tend to be on the rise year after year. Sepsis is also one of if not the leading expenses, and I know we've talked about the problem of using health care expenses especially in the US because our healthcare system is so skewed in terms of how much everything costs, but sepsis costs the US healthcare system billions and billions of dollars every year.
Erin Welsh	I mean at the very least it seems like it would be a good proxy for the number of days that you spent in the hospital, the number of different specialists that need to see you, etc.
Erin Allmann Updyke	Exactly. So as one one example from a paper they cited that in 2013 sepsis cost the US over $24 billion in total hospital expenses which is 13% of total US hospital costs.
Erin Welsh	Whoa.
Erin Allmann Updyke	Even though sepsis accounted for about 3.5% of hospital stays. So it's disproportionate, the cost, to the amount of total hospital stays.
Erin Welsh	Wow, okay.
Erin Allmann Updyke	Yeah. Because it can be such severe infections.
Erin Welsh	Yeah.
Erin Allmann Updyke	When we try to look more globally I think what we really have to understand is just how underestimate these numbers likely are, the true scale of sepsis in the US but also especially in low and middle income countries across the globe, we really don't have a handle on the global burden. A paper from 2017 estimated about 49 million cases worldwide.
Erin Welsh	Wow.

Erin Allmann Updyke	And 11 million sepsis-related deaths. If those numbers are accurate, again these are estimates, that would be almost 20% of all global deaths. The vast majority of which it's estimated 85% of those sepsis-related deaths are in low and middle income countries that we just aren't getting good data on. It's just so horrific.
Erin Welsh	Yeah, it truly is.
Erin Allmann Updyke	And it's also estimated that almost half of all these cases occur among children. So 20 million cases among children and 2.9 million global deaths in children under age 5 is what this paper is estimating. So it's a huge health care problem, it's difficult to diagnose, again the mortality rate can vary quite a lot. Some papers just that try and estimate it overall say anywhere between 1/3 and 1/6 people with sepsis can die. And so the World Health Organization has understandably made this a huge campaign and and a priority as well as the Surviving Sepsis Campaign that I mentioned already. One of the big things that the Surviving Sepsis Campaign tries to do in addition to raising awareness is also just gathering data and analyzing that data in a way to try and actually improve outcomes. And one of the big issues with the data that exists so far is that it generally comes from very high income countries and so we have to recognize the limitations in how we can interpret and then apply that data to much less resource rich areas.
Erin Welsh	Yeah.
Erin Allmann Updyke	Right? And importantly all of these kind of campaigns and policies are largely like I said trying to improve outcomes as well as improve our recognition of sepsis and how we treat it to reduce morbidity and reduce mortality. Sepsis is something that has likely always been with us and will likely always be with us. And so it's not something that there are large groups saying we should eliminate sepsis entirely, that's not realistic goals, at least not at this point. And one I think of the reasons is how little we still understand about sepsis, Erin.
Erin Welsh	It's shocking but also not shocking.
Erin Allmann Updyke	There was a great paper from The Lancet Infectious Disease 2019 that was written by people from the European Group on Immunology of Sepsis, EGIS, loved it. And they were really upfront about their feelings on all of this. They basically were like look, the reason that we have all these different definitions and all this controversy of is it this criteria or that criteria, etc, is because we just don't understand the immunology of sepsis. We don't, we do not understand it. And so this article really laid out what they feel at least are the major deficits in our understanding and where we should go from here. They did this by looking at three different stages of sepsis. Before it develops, which is my favorite stage to think about.
Erin Welsh	Very important.
Erin Allmann Updyke	Who is at risk? Why are they at risk? What kinds of research do we even need to do to better understand this initial process and these specific risks to be able to actually prevent sepsis to begin with?
Erin Welsh	Maybe change up the animal models we're using?

Erin Allmann Updyke	Yes, we don't have good animal models for sepsis. Then we also have the next stage, the evolution of sepsis. What are these specific immune processes that are underlying this organ damage and how might we use these to better target treatments? There have been a lot, mostly of animal model studies, of well if IL-10 is involved, let's affect that, like these specific immune modulators. And the short answer is they don't work, right, because these are too broad. So anything that we have tried to do to modulate the immune system ends up making things worse rather than better when it comes to sepsis so far. And finally the third stage, post sepsis. What are the consequences of having a severe sepsis infection in the long term? And what can some of these consequences teach us about the underlying pathology of sepsis? We don't have answers to those but I think it's just kind of a nice framework to think about where we can go from here.
Erin Welsh	Yeah. It's good to have questions. You have to have direction.
Erin Allmann Updyke	Exactly.
Erin Welsh	Yeah.
Erin Allmann Updyke	So it is going to be very interesting to see how these definitions continue to change and how treatments then continue to change.
Erin Welsh	I have a question about something you said about numbers going up.
Erin Allmann Updyke	Yeah.
Erin Welsh	Is that an apparent increase? Is that a real increase? What do we think about that?
Erin Allmann Updyke	I don't know if we know.
Erin Welsh	Okay.
Erin Allmann Updyke	Yeah. I don't know if we know. Is it because of changing definitions? And so are we broadening our definition in order to capture people at an earlier stage to then prevent severe infection? Or are people actually coming in with sepsis and sicker? I don't have a great answer to that.
Erin Welsh	Another question I had is if you have had sepsis one time and recovered, are you more likely to develop sepsis a second time?
Erin Allmann Updyke	That's a very good question. I think it probably in large part depends on what the inciting factor was. If you have cancer and you are immunosuppressed and you end up getting an infection that leads to sepsis and you recover from that but you still have cancer and you're still immunosuppressed then yes, you're still at high risk for sepsis. If you got a cut and a wound that was infected and you ended up with sepsis but you don't have any other underlying immune conditions that we know of, of course there's so much individual immune response differences that we just don't know about, it's a good question as to whether you are at higher risk or not. I think we don't probably know enough to know in those instances.
Erin Welsh	Okay, that makes sense.
Erin Allmann Updyke	Yeah, great question though. That's very interesting. Any other questions, Erin?

Erin Welsh	I mean a million.
Erin Allmann Updyke	Like do we even know what sepsis is at the end of this?
Erin Welsh	I'm not sure that I do besides the very broad definition but it seems like a moving target.
Erin Allmann Updyke	Yeah.
Erin Welsh	And impossible to pin down right now.
Erin Allmann Updyke	Yeah.
Erin Welsh	Maybe the future. The future holds all the answers.
Erin Allmann Updyke	For sure. It is also probably interesting to think though about so many things now that maybe are more specific definitions that used to have just been called under a catch all of sepsis.
Erin Welsh	Yes.
Erin Allmann Updyke	So I do wonder how many other things might come out of our current definition of sepsis.
Erin Welsh	Right. We have a bowl that is sepsis and we can draw out little bits of paper that say oh, that was actually, I don't know any of the things.
Erin Allmann Updyke	Right.
Erin Welsh	But we now call that something else that is not sepsis.
Erin Allmann Updyke	Yeah.
Erin Welsh	Yeah.
Erin Allmann Updyke	Interesting. Anyways, sources?
Erin Welsh	Sources. I have a few papers that talk a little bit more about the changing definitions of sepsis and the more recent history of sepsis if you'd like to check those out. But let me just shout out again the fantastic book by Lindsey Fitzharris 'The Butchering Art' all about Lister, all about early surgery, all about how germ theory kind of came to save the day a little bit and Lister. It's such a great read.
Erin Allmann Updyke	It is really great. I can also recommend. I had a number of sources. Not as many as sometimes because the papers that I found were actually really comprehensive just on the overall definitions and what we know so far about the immunology of sepsis. So I will post those as well as the list of all of our sources from every single one of our episodes on our website thispodcastwillkillyou.com under the EPISODES tab.
Erin Welsh	Thank you again so much Katy for taking the time to chat and sharing your story. It really means a ton. And we will also link to some more articles that Katy has shared as well as the Sepsis Alliance website which is sepsis.org. So be sure to check out the sources for this episode and also the show notes.

Erin Allmann Updyke	Thank you also to Bloodmobile who provides the music for this episode and all of our episodes.
Erin Welsh	And thank you to Exactly Right.
Erin Allmann Updyke	And thank you to you, listeners. We hope you enjoyed this episode.
Erin Welsh	Yeah, we hope you found it interesting. What are your burning questions about sepsis still at the end of this? Let us know.
Erin Allmann Updyke	I have a lot.
Erin Welsh	Yes. And a special thank you as always to our wonderful, generous patrons. We appreciate you so, so very much.
Erin Allmann Updyke	Yeah, thank you.
Erin Welsh	Well until next time, wash your hands.
Erin Allmann Updyke	You filthy animals!