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INSIDE

MARCH 1999

VOL. 5, NO. 3 (pages 25-36)

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Can salmonella save lives? Human trials expected this spring

Early studies show attenuated bacteria stop growth of tumor cells

Years from now, medical practitioners may look back at this spring as a landmark in the race to find a cure for cancer. Human trials are expected to begin in the coming weeks on tumor-targeting altered salmonella bacteria engineered by Yale researchers in New Haven, CT. The research is funded by Vion Pharmaceuticals, also of New Haven.

Researchers "de-fanged" the bacteria by disabling the salmonella gene for the powerful toxin lipopolysaccharide so it would not cause food poisoning and the potentially life-threatening reaction it can trigger in the human body.

Researchers found the altered salmonella slowed the growth of melanoma tumors in mice and later in a variety of malignant tumors in pigs.

"The discovery has changed all our lives," says **John Paweleck**, PhD, senior research scientist at Yale's dermatology department, and **David Bermudes**, PhD, Vion's associate director of biology and adjunct assistant professor at Yale.

Paweleck, Bermudes, and their research team made the discovery while experimenting with bacteria as a delivery system for a variety of anti-cancer agents, since researchers have long thought certain bacterial

KEY POINTS

- Vion Pharmaceuticals in New Haven, CT, petitioned the FDA to begin human trials on genetically altered salmonella bacteria and its effect on malignant tumors.
- Early studies by Yale researchers show a 90% reduction in tumor growth with a one-time injection of altered salmonella bacteria.
- "De-fanged" salmonella is being considered as a delivery mechanism for other drugs.

infections seem to help cancer patients survive longer. The bacteria were then implanted subcutaneously in mice with melanoma tumors. What they discovered was "tremendously exciting," Paweleck says.

Salmonella seeks out tiny tumors

The bacteria spread through the circulatory system and multiplied, stunting tumor growth within 24 hours but not triggering the extreme white cell alarm reaction responsible for the septic shock that kills organisms infected with wild salmonella.

"Salmonella seeks out cancers in the body. It travels through the blood stream and finds any tumor, even those too small for us to know about," says Bermudes. "That is its beauty. We don't have to target a specific location since it can even seek out small tumors which are metastasizing."

"Salmonella loves tumors," says Paweleck. "It seeks out a safe harbor in tumors; places with little circulatory systems which typically escape drug therapy."

Paweleck and Bermudes think the salmonella slows tumor growth in part by competing with malignant cells for the essential nutrient, adenine. They also theorize the suppression may be due to the salmonella's stimulation of the immune system, among other possibilities.

In early trials, mice with melanoma tumors in the control group died within four weeks, but the salmonella-inoculated mice lived three to four weeks longer. Later studies in pigs found similar results with malignant breast, lung, and colon tumors.

Current generations of the salmonella strain are keeping the mice alive five times longer than the control group, and Bermudes says the second generation is expected to be more potent with an even smaller dose of the bacteria.

Paweleck says they observed no side effects, a stark contrast to the common side effects of other treatments — nausea, weight and hair loss.

"You can inject a 20-pound pig with 10^9 salmonella cells, and the animal wouldn't even notice it," Paweleck says.

Usually reserved researchers are enthusiastic about the development.

"We have high hopes in this area. I am watching it closely," says **Debabrata Banerjee**, PhD, a molecular pharmacologist at Memorial Sloan-Kettering Cancer Center in New York City.

Banerjee says the laboratory work and animal trials on the altered salmonella have been "very thorough," and he laid to rest his early fears that the salmonella might revert to its toxic state.

Bermudes admits the team was concerned about its reversion during early trials, but it hasn't happened.

"Even if it did get out of control, salmonella poisoning is easily treated with a wide variety of antibiotics," he says.

Vion expects FDA approval for Phase I trials in the first quarter of 1999, Bermudes says.

The trials will focus on patients with melanoma who will be given one injection of altered salmonella and monitored over a period of time. Later trials will likely include colon and breast cancers, he says.

For more information, John Paweleck can be reached at (203) 785-3078, and David Bermudes can be reached at (203) 498-4210. ■

AMA urges wider use of beta-blockers

Drug benefits outweigh risks

It's no secret beta-blockers are enormously successful in preventing a second heart attack or sudden death.

Or is it?

The American Medical Association (AMA) in Chicago thinks it's a well-kept secret.

For the first time in its 151-year history, the AMA marshaled its resources and teamed with

COMING IN FUTURE MONTHS

- Setting exercise goals with your heart failure patients
- Sounding the red alert to prevent pediatric asthma fatalities
- Helping monitor symptoms with adult day care
- Diabetes management: A major concern in minority populations
- Using a formal program to assess your asthma patients needs

KEY POINTS

- The American Medical Association (AMA) and other specialty associations urge wider use of beta-blockers for patients who have had acute MIs.
- Beta-blockers may help prolong the lives of many patients with asthma, diabetes, obstructive pulmonary disease, and other illnesses.
- AMA says benefits outweigh risks of complications for patients with the above conditions.
- *Quality Care Alert* was sent to 170,000 physicians nationwide.

five other professional associations last December to send out a nationwide alert to 170,000 physicians, recommending the use of beta-blockers for patients who suffered an acute MI.

Contraindications are not absolute

Beta-blockers already account for 5.5% of prescriptions dispensed in the United States, according to IMS Health, and independent pharmaceutical tracker in Plymouth Meeting, PA. For every 1,000 U.S. HMO members, 192 prescriptions for beta-blockers are written.

Also for the first time, the AMA says the benefits of beta-blockers outweigh the risk for conditions for which the drugs were previously contraindicated.

Departing from a long-standing caveat against prescribing beta-blockers for many patients with asthma, diabetes, obstructive pulmonary disease, severe peripheral vascular disease, PR intervals greater than .24 seconds, and moderate to severe LV failure, the AMA says "there is evidence to suggest that many of these patients will benefit from beta-blocker therapy," but "decisions should be made on a case-by-case basis."

In the past, many physicians believed the contraindications were an "absolute," says **Percy Wootton**, MD, past president of the AMA and clinical cardiologist practicing in Richmond, VA.

"Beta-blockers can be used safely by many of these patients when closely followed by a physician," Wootton says.

It's a matter of practice catching up with science, the experts say.

"This is based on scientific knowledge," says Wootton. "We know beta-blockers increase long-term survival up to 40% after acute MIs.

"Cardiovascular disease is still the No. 1 killer of both women and men. Beta-blockers are dirt cheap and just as common as dirt, so our goal is to get people to use them."

"We wanted to bring it to the attention of general practitioners that beta-blocker prophylaxis has an important role for many patients who are post-MI," says **Herbert Young**, MD, director of the scientific activities division at the American Academy of Family Physicians (AAFP), one of five major medical associations who issued the alert.

"All of us are in agreement," Young says. "The science is good, but the practice needs to be improved."

Use of beta-blockers evolving

The scientific community validated the importance of beta-blockers over the decade or more they have been in common use.

"It is an evolutionary process," Young says. "Now the science is solid; we need to get the information to the physicians when they need it."

Why aren't more physicians already prescribing beta-blockers?

"It's incredible that family practitioners wouldn't know about beta-blockers; they've been around so long," says **Jackie Williamson**, MD, a family practitioner in Woodstock, GA.

Williamson suggests there may be other reasons why family practitioners don't prescribe beta-blockers:

1. Most patients with heart attacks are discharged from the hospital by a cardiologist, and the cardiologist would prescribe the medications. Most family practitioners are reluctant to override the wishes of a specialist.
2. Beta-blockers have been around for a long time, but there are new kids on the block, like ace-inhibitors and calcium channel blockers, that are just as effective and may not have some of the unpleasant side effects of beta-blockers.
3. Side effects are a problem, particularly the sexual dysfunction sometimes connected with the use of beta-blockers, Williamson says. "It may be that some doctors don't want to use them for that reason or patients won't take them anyway if sexual dysfunction becomes a problem."

This first *Quality Care Alert* is seen as only one step in a larger effort to increase physician and patient awareness of the efficacy of beta-blockers.

"It's a small step in a complex process," Young

says. "We need to bring knowledge to people repetitively through a variety of channels. This one mailing isn't the end-all."

"We're following the learning model that says you have to tell somebody something three times," Wootton says.

Reminders of the beta-blocker alert will be added "as a postscript" to other alerts in the coming months. An alert on pneumococcal vaccine was planned for late February or early March.

While experts say some patients are not good candidates for beta-blockers, Wootton says primary care physicians need to "use their judgment" to determine the severity of the disease and weigh the risks.

He advises them to monitor patients for a variety of possible complications, including indications of constriction of peripheral arteries or prolonged PR intervals through ECGs and physical monitoring.

The unprecedented year-long collaborative effort between the AMA and the other associations "recognizes that all of medicine has a challenge," says Young. "No specialty is out there where we'd like it to be. Our focus should be on improving care for all patients, not bickering among specialties."

Wootton and his AMA colleagues hope the alert will also encourage patients to ask their doctors about beta-blockers.

"As a physician, I have absolutely no problem with a patient saying, 'Doctor, shouldn't I be on beta-blockers?' I am a firm believer in educating patients," he said.

For more information, Percy Wootton can be reached through the AMA at (312) 464-5000; Herbert Young can be reached through the AAFP at (800) 274-2237. ■

Early detection of coronary calcium can save lives

Experts press for wider use of EBCT as marker

A test that will detect markers for coronary heart disease earlier than any other test — a good thing, right?

Definitely, say some experts.

Probably, says the American Heart Association (AHA).

Electron-beam computerized tomography, or EBCT, measures coronary calcium and has the potential to motivate thousands of patients to save their own lives, says **Daniel Berman**, MD, FACC, chief of cardiac imaging at Cedars-Sinai Medical Center in Los Angeles, which has one of about 60 of the $1.5 million highly advanced CT scanners in the United States.

EBCT guidelines are changing

The AHA is currently broadening its 1996 guidelines on coronary calcium scans to reflect the latest information: Coronary calcium can be a marker for atherosclerosis. Old guidelines only called for EBCT for patients who complain of chest pain — particularly if the pain is atypical of coronary artery disease (CAD).

Berman thinks that is far too conservative.

"Half of coronary artery disease presents itself as sudden death or irreversible MI," he says. "Saving lives means saving heart muscle by defining the disease earlier than any other test. That's what the EBCT does."

So far, so good, says **William Stanford**, MD, an AHA spokesman involved in re-writing the guidelines and a radiology professor and chief of chest and cardiovascular radiology at the University of Iowa College of Medicine in Iowa City.

"The greater the calcium, the greater the chance for a cardiac event. These things are all pretty well accepted," Stanford says.

Stanford says he would not personally oppose

KEY POINTS

- Electron-beam computerized tomography (EBCT) measures of coronary calcium provide a possible early warning device for coronary artery disease (CAD).
- Test is recommended by many doctors for patients with one or more risk factors for coronary artery disease.
- The American Heart Association is currently broadening its guidelines on the EBCT.

an EBCT for any patient with one or more risk factors for CAD:

- obesity
- smoking
- high cholesterol
- high blood pressure
- diabetes
- family history of heart disease

However, the AHA says more outcome data need to be presented to substantiate that coronary calcium is a predictor of cardiac events.

"There is still a considerable amount of controversy," Stanford says.

More studies needed

There certainly is controversy surrounding the procedure for several reasons.

The subject of EBCT is treated at some length in two studies, a letter to the editor and an editorial the Dec. 31, 1998, issue of the *New England Journal of Medicine.*

While saying EBCT is a "promising" and even "exciting" new diagnostic tool for patients with suspected coronary artery disease "that may contribute to overall risk assessment," the *NEJM* recommends more studies.

"Before routine clinical use of coronary CT scanning can be recommended for screening of asymptomatic patients or for the evaluation of patients with chest pain . . . more . . . basic studies are required to define the role of calcium in plaque stability and progression . . . and to demonstrate the cost effectiveness of these techniques and their potential impact on cardiovascular outcomes."

That issue of the *NEJM* features a 149-patient study from the Electron Beam Tomography Research Foundation and Vanderbilt University in Nashville, TN, which shows decreased volumes of atherosclerotic plaque when patients were treated with HMG-CoA reductase inhibitors, and the resulting serum LDL cholesterol levels for at least 12 months after an EBCT showing the need through a calcium-volume score.

A German study published in the same issue shows unevenness in the image quality, but concluded "when image quality is adequate, electron-beam CT may be useful to detect or rule out high-grade coronary artery stenoses and occlusions."

A letter to the editor from two physicians at Walter Reed Army Medical Center in Washington, DC, questions "centers performing electron-beam CT (that) advertise and generate business on the basis of patients referring themselves for the test."

Test isn't cheap

Berman doesn't think everyone — even those with risk factors — ought to have an EBCT.

"I think those who are at risk and not doing anything about it should have the screening," he says. "If they're already doing everything they can, I wouldn't recommend it."

The test is expensive (about $400 at Cedars-Sinai), and most health care providers will not cover the cost.

Berman believes the key to the value of the EBCT is that it buys time where it counts — on the front end of the disease.

If CAD is caught early enough, Berman says, it can be stopped in its tracks with a combination of lifestyle changes and drug therapy as shown in the Vanderbilt study.

"We know that the very first thing that happens with CAD is the development of fatty streaks in the lining of the arteries. There's no calcium then — that may not be visible for some years — but over a period of years, the atherosclerosis plaque becomes larger and ends up obstructing the vessel," Berman says.

Motivating patients to change habits

He advocates the EBCT because it can detect occlusion of the artery from virtually zero percent, compared to a variety of other cardiac tests, such as stress ECGs and stress-thallium studies, which may not detect occlusions until the artery is 50% blocked or more, and the opportunity for a good outcome may be impaired or even lost.

An EBCT that shows the early markers for CAD is a powerful motivator for lifestyle changes, Berman argues.

"Just think about it. If you tell somebody their behavior puts them at risk for a disease they may or may not get unless they change their lifestyle, you're not likely to get much response," Berman says. "But if you tell them they already have the earliest signs of the disease, which can be stopped before it becomes life threatening, they are much more likely to do what they need to do."

While the 1996 AHA guidelines recommend the EBCT only for patients already experiencing chest pain; even then panel members did not have any serious objections to the screening and conceded it "will be used as an early warning system for certain groups because it is simple to

do, non-invasive, takes only a few minutes, and is comparable in cost to other tests."

Many insurance companies, including the giant Prudential Health Care in Roseland, NJ, don't pay for the test because they still question its value, according to **Arthur Levin**, MD, Prudential's chief medical officer.

"We don't cover the EBCT for screening," Levin says. "We don't really think that just because you show calcium it means anything. There is no consensus about it's value. The procedure remains controversial."

Levin adds that EBCTs may be covered by his company to evaluate patients complaining of atypical chest pain.

For more information, Daniel Berman can be reached at (310) 855-4224; William Stanford can be reached at (319) 356-3393. ■

Researchers seek success with mechanical pumps

Can devices span CHF, recovery?

The day is coming, researchers say, when mechanical pumps will offer CHF patients a range of options for improvement and recovery.

Refinements continue to be made in using left-ventricular assist devices (LVADs) as a bridge to transplantation. Investigators now want to find out how they can offer the devices to more patients — such as those who are not transplant candidates because of their advanced age or degree of heart disease.

And today's tantalizing but rare cases of patients being weaned from their LVADs hint at a time in the future where doctors can use a pump to let a failing heart rest and heal until it can work well on its own again.

Getting to these goals, and crossing what some doctors call "a bridge too far," means pushing the limits of the technology and running the trials. Investigators are optimistic.

"You might decide that today's pumps are not right for you and your patients," says **Mehmet C. Oz**, MD, an LVAD researcher and cardiothoracic surgeon at Columbia-Presbyterian Medical Center in New York City.

"With the advances being made, you should see a pump that's right for you within a decade," he explains.

KEY POINTS

- Left-ventricular assist devices (LVADs) are considered bridges to transplantation.
- Researchers are working to make LVADs available to patients who are not eligible for transplantation.
- In rare instances, patients using an LVAD regain heart performance and can undergo explantation, but researchers are just beginning to understand cardiac remodeling and damage on the cellular level and whether or not it can be reversed.

Buying patients more time as they await transplantation is a huge niche for LVADs to fill. Recent published reports determine only 2,500 organs are available each year to some 60,000 patients who need them or some type of mechanical help. In 1996, more than 10% of the transplantation candidates died waiting for a new heart.

What about those not up for transplants?

Oz says doctors should be thinking about when LVADs may be appropriate for their patients today, whether or not they're on the transplant list.

"The first rule of thumb is that no one should die of heart failure without being considered for heart pumps."

That doesn't mean giving one to every patient, Oz notes, but rather, thinking about how a patient can be treated with an LVAD after traditional therapies are ruled out with a line of questioning such as the following:

1. **Does the patient have a problem that can be repaired, such as aortic or mitral valve disease or an aneurism?**
2. **If there isn't a physical defect that can be targeted for repair, can the patient's heart failure be controlled with medication?**
3. **If medication cannot keep the patient's condition stable, could transplantation be implemented to reverse the patient's declining cardiovascular performance?** (In this case, a heart pump can help sustain the patient until a permanent organ becomes available.)
4. **If the patient is not a transplantation**

candidate, could an LVAD be used? (Today, patients can be part of the clinical trial testing the devices when other options are not appropriate or can no longer be helpful by themselves.)

This last consideration may not sit well with some doctors, who may feel that if a patient is not up to the surgery and recovery from transplantation, he or she would not benefit from using an LVAD.

Oz says his team is learning how LVADs can be helpful to these patients. The researchers have a $7 million government grant for their REMATCH study (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart failure). He says patients have to apply to participate in the study, but for those who are not transplant eligible, an LVAD may provide a treatment option.

How long on an LVAD?

Two end points in heart pump therapy are crystal clear:

- transplantation
- infection requiring removal

In other cases, knowing when to stop using the LVAD is not as certain. Oz says there will be a growing number of patients not going on to transplant who will continue with their device, incorporating other treatments such as surgery and drug therapy to improve their heart performance.

Researchers also are looking at the chances of using the LVAD to help the patient's own heart recover enough to work on its own. This role is called a bridge to recovery.

In 1997, German investigators reported in *Circulation* (1997; 96:542-549) that they were able to wean a third of their 17 patients from their LVADS.

"We haven't been able to reproduce their results," Oz says. In a recent article in *Circulation* (1998; 98:2,383-2,389), his team reported a retrospective study and an explanation evaluation that used exercise tolerance as an indicator of success.

The team found that among 111 LVAD recipients being bridged for transplants since 1991, only five were explanted. In three of these instances, the devices were removed because of infection. The other two patients had their LVADS removed because they were not going on to transplantation: one after 186 days and another after two years.

Of these five explant cases, two died three months after explantation. Two patients needed reimplantation after being without them — one after two years, the other after 170 days. The fifth patient was still alive in class I CHF after 15 months without the device.

In the second part of the study, 39 recent LVAD recipients were considered for explantation, according to how well they could exercise with their LVAD output reduced to 20 cycles per minute. Seven of the 39 patients were able to exercise at this rate of assistance and still keep stable hemodynamics. One was able to be explanted.

Oz says the Germans' success may be due to the way Europeans wean their patients off the LVAD three months after implantation. The practice may be a good idea because researchers still have a lot to learn about how the heart responds to its mechanical helper and how long the partnership should last.

It's possible that patients reach a point where the heart pump no longer works well with the compromised heart. A device could even cause atrophy in the heart muscle, depending on its synchrony with the ventricle as it contracts and relaxes.

Research will bring more uses for device

More research is needed, Oz says, to determine how long a patient should use the heart pump, whether or not weaning should begin, and how weaning should be done.

Right now, he says his team does not implant LVADs with the intention of weaning patients off of them. Nearly all the heart pumps used now are bridges to transplantation. Oz notes he recently had a case where a patient had a massive heart attack and an LVAD was used as part of his overall treatment, but those situations are not as common.

Other physicians see three standard uses for an LVAD, including helping patients who suddenly run into trouble, says **Ross Zimmer**, MD, a Philadelphia cardiologist with the joint heart failure program at Presbyterian Medical Center and the Hospital of the University of Pennsylvania.

These uses are:

- A device can sometimes help patients who suffer complications during surgery.
- An LVAD is used as a transplantation bridge (the most common use).
- LVADs are used in a clinical trial.

The editors commenting on Oz's study in *Circulation* note they hoped clinicians would one day be able to assess how a failing heart has been damaged on a cellular level — and whether the

damage is reversible. This would give clinicians an indication of which hearts may go on to heal if given some mechanical assistance.

Oz says it would be even more helpful to understand the cellular changes of the heart so they can be reversed long before treatments like heart pumps are needed. Answers may come from looking at how patients may not be metabolizing free fatty acids or calcium properly. Harvesting heart tissue from deceased CHF patients could allow scientists to probe the mitochondria and hunt for missing or defective genes, which could lead to a whole new arsenal of cardiovascular genetic therapies.

Until that point, doctors say LVADs have a role in treating CHF.

"I hope that as [LVADs] become more common, they are developed not just as a bridge but as an alternative to transplant," says **Jim Fitzpatrick**, MD, clinical assistant professor of medicine in the division of cardiology at Thomas Jefferson Medical Center in Philadelphia. "The economics are staggering."

He says last year, Jefferson implanted two LVADs into CHF patients as bridges to transplantation. The site is not a transplantation center, so the patients continued with treatment at other centers to get new hearts.

And patients can find some reassurance when they learn that LVADs can help during the wait for a heart, says Zimmer: "It's nice psychologically for patients to know that it's there."

Editor's note: For more information about the LVAD study and to learn how to become involved, call (888) REMATCH. ■

Your patients can regulate their diuretics at home

The key is giving them clear instructions

Can your patients regulate their diuretics according to their daily weigh-in? It takes some specific instruction about what they should do every day and how to react when they are gaining weight from fluid retention. But doctors say what patients know how to do at home can do a lot to keep a handle on their condition.

"I think it's an important part of managing the disease," says **Jay N. Cohn**, MD, professor of medicine at the University of Minnesota in Minneapolis and author of an article on the management of chronic heart failure (*N Engl J Med* 1996; 335:490-498).

KEY POINTS

- Patients can learn to regulate their diuretics at home if they receive clear instructions on how to maintain the ideal body weight determined by the physician.
- Home diuretic regulation requires the physician to know how well the drug works in each particular patient so both the appropriate daily medication and the restorative agent can be prescribed.
- Some physicians may prefer to use metolazone for the restorative diuretic, instead of extra doses of the daily loop diuretic.

"The day-to-day management of the diuretic is something patients can do at home," he says. "That tends to keep people out of the hospital, before they begin to decompensate. Anyone can be educated about his disease and how to manage his medication," says Cohn. "It's just like diabetic patients can be taught to regulate their insulin."

Keep medication routines simple

Self-regulation begins by establishing the patient's ideal body weight. Cohn says the ideal weight is where the patient is stable and has normal central venous pressure. "That is the weight you want to maintain," he says.

Then, give the patients simple instructions on what to do if they find they have gained two or more pounds since they weighed themselves the previous day. Usually it means taking more medication. "Often, patients have what's called a 'kicker,'" Cohn says. That's the extra medication taken to address the weight gain from fluid retention. When patients are taking a daily loop diuretic, their doctors may instruct them to take an extra one when their weight increases, until the ideal weight is restored.

When the weight goes down again, the patient may not remember to go back to the original dosage. For this reason, it may be easier for the patient to remember to keep the daily loop

diuretic constant and use a different medication as the kicker.

"I find it is easier to use metolazone intermittently, rather than change the loop diuretic, but that is an individual decision," Cohn says. He adds that it works like a thiazide, at a different level of diuresis. The kicker is taken until the patient returns to the ideal weight, then only the regular daily plan is followed again. Patients continue to take their daily diuretic as well, unless told otherwise by the physician.

Also, when choosing the diuretic, make sure you understand how it affects that particular patient and how much it takes to get the responses you're looking for, says **Jim Fitzpatrick**, MD, clinical assistant professor of cardiology at Thomas Jefferson Medical Center in Philadelphia.

This is true for both the daily dose and the kicker, he says. That way, doctors know the daily dose should be effective and the response diuretic will be able to start working on the extra fluid retention.

Fitzpatrick says he knows many patients who have been able to do this home regulation. He notes that some patients like to have a contact person to call at the doctor's office, such as a telemanager or a nurse practitioner, just to confirm they are doing the right thing. "They'll say, 'Here's what I weigh, and here's what I plan to do.'"

Cohn says doctors can cut down on those types of calls by giving the patients clear information and instructions during the office visit. Patients will know they are doing the right thing because it was discussed during the appointment.

What helps even more is to have the instructions written out so they don't have to commit it all to memory and call when they forget what to do. Then, by making daily weighing a part of the morning routine before getting dressed, at the same time of the day, they become comfortable with it. Deciding the diuretics to take for the day becomes as routine as the weigh-in.

More points to remember

Cohn and Fitzpatrick advise physicians to remember the following points:

- "When you have a patient with sodium retention, it is important to check serum electrolytes and renal function each month or every other month," Cohn says.
- When patients take the kicker, remember that potassium levels may drop. If they take a supplement to maintain potassium, they may need to increase that, too, or eat more fruit if they are maintaining levels with diet alone. Cohn says one banana, for example, has about 10 milliequivalents of potassium, about the same as a potassium supplement.

Potassium regulation is "a very individualized" thing, he says, therefore maintenance and response strategies must be tailored to each patient.

Patients may also lose potassium if they have diarrhea or have been vomiting, so instructions should cover these situations as well.

- Prepare the patient before starting the self-regulation regimen, says Fitzpatrick. The physician should make sure the patient is educated about the condition and is motivated to take some responsibility with the daily management of the disease.
- Remember to get a sense of how compliant the patient will be and how the diuretics will affect each particular patient. ■

Be on the lookout for depression

Don't let it creep up on your patients

It usually doesn't appear all at once, and there may not be a clear starting point where symptoms begin. But once it shows up, depression can unravel the gains you make with your congestive heart failure (CHF) patients.

With treatment plans depending so much on the patients remaining motivated — to keep up with drug therapy, appointments, and tasks such as daily weighing — depression can undo a lot of the control you're trying to get over their condition.

"The disease creeps up on people," says **Sue P. Heiney**, PhD, RN, CS, FAAN, a certified specialist in psychiatric nursing at the University of South Carolina in Columbia. "It's not like dealing with an MI, where there is a clear-cut event that puts a patient in crisis."

Heiney, who specializes in working with cancer patients, says she often lectures on depression for clinicians treating patients with heart failure because of the similarities with how patients deal with lasting illness and how depression can develop.

Patients who undergo surgery face an increased

KEY POINTS

- Depression is a common complication in treating patients with cardiac problems.
- Experts urge recognizing symptoms of depression, asking about quality of life issues, and initiating treatment.
- Psychotherapy or counseling alone is not enough to treat most cases of depression. Antidepressant medication is needed.

risk of depression, whether they are recovering from a valve replacement, cardiac bypass, or even transplantation. Depression can develop in patients who have been dealing with CHF only. What's needed, say experts, is to look for the situations that can lead to depression, find out if the signs are there, then go ahead and treat it.

Don't wait for one signal to jump out at you as though someone flipped on the depression switch. CHF patients show the gradual symptoms much the way other patients do.

"It's simple to assess, but it just gets ignored," Heiney says. "We often get so wrapped up with assessing symptoms and disease management that we miss the quality-of-life issues."

"Patients come in to get an EKG, a check of medical symptoms, heart symptoms — but doctors just need to know that the risk of depression is there," says **Jim Fitzpatrick**, MD, clinical assistant professor of medicine in the division of cardiology at Thomas Jefferson Medical Center in Philadelphia.

He says half of the patients who have had heart surgery show signs of depression. "In patients with heart failure, they may have had surgery for valvular repair or a bypass. After those surgeries they are in a high-risk group."

It is helpful to recognize that just being a heart patient is a roller coaster ride of emotions for most people.

"They've been sick. There was the anticipation of surgery. They go have it done. Then they still don't feel well. They made it through, but instead of having a sense of relief, depression sets in," Fitzpatrick says.

The same pattern is true for patients who undergo transplantation, says **Mary Amanda Dew**, PhD, a professor of psychiatry at the University of Pittsburgh Medical Center.

Before the transplant, there is a lot of stress for patients and their families. "Nobody is really sure if they are going to make it," she says. "People live in this limbo of not going to know what's going to happen. It goes on and on."

Reality hits after surgery

Dew, who works with cardiovascular patients, says she has studied depression in heart transplant patients for 10 years. The emotions can continue to work on the patient after surgery, especially after the patient's relief that he or she survived the procedure wears off.

"After the transplant, there is disappointment. We've found that people come down off of a honeymoon period," she says. "People aren't doing as well as they thought they would do."

If the patients go on to develop depression, Dew says studies show they are more likely to develop complications like cardiac allograft disease.

"That's something seen across the board," she says, noting it worsens the health status of transplant recipients and bypass patients alike. Complications have such a strong tie to depression, she says, that it is a powerful predictor of physical morbidity.

Heart failure symptoms can mask some indications of depression. For example, patients may have less energy and probably can't be as active as they were when they were healthy. Those changes in a person's life could in time lead to depression. The signs that it's developing, such as fatigue or difficulty sleeping, may appear to be just from the CHF itself.

"Probably, the question to ask is, 'How is your disease right now affecting your quality of life?'" Heiney says. "Then listen for the responses you get."

Start looking for symptoms

If you begin to hear about vague pain, headaches, or sexual problems, start being suspicious. After some digging, you may determine a few of these symptoms are not indicating depression, but these are good places to start.

"Look if there are more complaints than usual," says **Jeffrey E. Kelsey**, MD, PhD, assistant professor of medicine and director of the Mood and Anxiety Disease Clinical Trials Program at Emory University's department of psychiatry and behavior in Atlanta. "Where we get a lot of hits are changes in sleep, appetite, energy, concentration, or feeling blue."

"Look for clusters of symptoms that are suddenly appearing," Dew says.

They can be both somatic (such as eating and sleep habits) and cognitive, such as sudden difficulty in decision making, feelings of worthlessness, or thoughts that they or their families would be better off if they died. "Some people may show one type or the other," Dew says. "Look for both."

Kelsey notes that elderly people tend to complain more about physiological symptoms than psychological ones.

But that doesn't mean that psychological ones aren't there. In these cases, it may help to talk with the patient's spouse or another family member to see if they have noticed problems such as increased irritability or changes in sleeping or eating habits.

Fitzpatrick says he had a patient's wife come to him to ask what could be wrong with her husband. She said her husband seemed so down after his surgery.

The patient went through the surgery well and made no complaints himself. His wife, however, told Fitzpatrick he wasn't sleeping well. He also had lost his appetite and had anhedonia, or no sense of pleasure in anything. With that information, Fitzpatrick started the patient on antidepressant medication, and he responded well.

Dew has one more note about the patient's household caregivers: Keep an eye on the patient's family. You may need to assess if they are showing signs of depression, too. If so, they may need to be directed to get help from their physicians.

"The caregiver and the patient tend to feed off of one another," she says. It's a big problem to your case when caregivers, who are usually under a lot of strain themselves, are the one who give the patient daily medication. "If they get depressed, they may not be able to do what they used to do."

Start with basic questions

So the physician is asking questions about quality of life, eating, sleeping, and overall mood — and a patient shows signs that depression could be a problem. "Chances are, you'll want to take a clinical history and evaluate specifically for depression," Heiney says.

The basics include asking about previous history with depression, suicide attempts (personal or family members), persistence of feeling down all day long and every day, and not enjoying their usual activities. Most doctors are familiar with this drill for patients who are not suffering chronic disease, but it is still valid to CHF patients as well.

"The yeses you get from these questions are a major red flag," she says. Then once the physician establishes the cause for depression and determines depression does exist, patients can be treated.

"Whenever you see signs of depression, go ahead and treat it," Kelsey advises. Some treatment begins at looking at the medication the patient is taking already. Some drugs can cause depression as a side effect, particularly ones that have a long half life and tend to accumulate in the body over time. ■

Disease State Management (ISSN# 1087-030X) is published monthly by American Health Consultants®, 3525 Piedmont Road, Building Six, Piedmont Center, Suite 400, Atlanta, GA 30305. Telephone: (404) 262-7436. Periodical postage paid at Atlanta, GA 30304. POSTMASTER: Send address changes to **Disease State Management**, P.O. Box 740059, Atlanta, GA 30374.

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Hours of Operation: 8:30 a.m.-6 p.m. Monday-Thursday; 8:30 a.m.-4:30 p.m. Friday, EST.

Subscription rates: U.S.A., one year (12 issues), $429. Outside U.S., add $30 per year, total prepaid in U.S. funds. One to nine additional copies, $215 per year; 10 or more additional copies, $129 per year. Call for more details. Missing issues will be fulfilled by customer service free of charge when contacted within 1 month of the missing issue date. **Back issues**, when available, are $38 each. (GST registration number R128870672.)

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Rezulin can cause liver failure in diabetics

Complications can be reduced with monitoring

Physicians have been warned to monitor liver functions of Type II diabetics using Rezulin (troglitazone), easing the alarm over liver failure and even death among patients using the anti-insulin-resistance drug.

Richard Kahn, PhD, chief scientific and medical officer of the American Diabetic Association in Alexandria, VA, says new labeling included with the drug since July by its manufacturer, Parke-Davis, a division of Warner-Lambert Co. in Morris Plains, NJ, "minimizes the likelihood of adverse side effects and liver disease" from troglitazone.

"We think the benefits outweigh the risk, if the recommended testing is followed," Kahn says, echoing a statement issued by the U.S. Food and Drug Administration (FDA) in early December. He dismisses a Dec. 7 *Los Angeles Times* report highly critical of Rezulin, the approval and marketing tactics used for the drug, and the "potential conflict of interest" on the part of Richard C. Eastman, MD, the National Institutes of Health's top diabetes researcher.

Rezulin is currently being used by approximately 1 million Type II diabetics, with sales for Warner-Lambert approaching $1 billion, according to the *Los Angeles Times* article.

Troglitazone was hailed as a great new drug of our time when it first came on the market in March 1997. By December of that year, deaths began to be reported among troglitazone users in Great Britain, and Glaxo-Wellcome withdrew its application for European approval of the drug. Shortly thereafter, the U.S. FDA issued a warning about potential liver dysfunction among patients using the drug and recommended liver monitoring five times a year.

In June, the National Institutes of Health (NIH) removed troglitazone from a study of non-diabetics after the death of a patient who needed a liver transplant.

In July, the U.S. consumer advocacy group Public Citizen petitioned the FDA to withdraw troglitazone from the market after 26 deaths from liver failure and three reported liver transplants among troglitazone users. The same month, Parke-Davis issued a "Dear Health Care Professional" letter urging frequent liver monitoring for patients using the drug.

Parke-Davis now says serum transaminase levels should be checked before a patient begins taking Rezulin, and levels should be re-checked "monthly for the first eight months of therapy, every two months for the remainder of the first year, and periodically thereafter."

The manufacturer also states, "Rezulin should be added to, not substituted for," sulfonylureas or insulin or as an adjunct to diet and exercise control.

Parke-Davis: 'Data show it is safe'

The company's studies showed a 600 mg daily dosage of Rezulin plus glyburide was most effective in long-term glycemic control.

"Liver disease is not a problem from our perspective. The clinical data show it is safe," says **Howard Foyt**, MD, PhD, director of clinical research, diabetes, and metabolic disorders at Parke-Davis in Ann Arbor, MI. "We don't anticipate major future problems with liver dysfunction. We think the labeling took care of it." ■