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RETURN SERVICE REQUESTED

PREDICTING NEUROLOGIC RECOVERY AFTER IN-HOSPITAL CARDIAC ARREST

In-hospital cardiac arrests are common and despite huge expenditures of effort and emotion, are often ultimately unsuccessful. It is difficult to predict meaningful survival (i.e. neurologic recovery) during the emotionally charged atmosphere of advanced cardiac resuscitation, but Paul Chan et al, *Arch Intern Med*, 2012, identified 42,957 patients across 551 hospitals between January 2000 and October 2009 who were successfully resuscitated following in-house cardiac arrest. Using multivariate logistic regression, a simple prediction tool was developed for favorable neurologic recovery following cardiac arrest. Eleven variables associated with favorable neurologic recovery were: young age, initial cardiac rhythm consistent with ventricular fibrillation or pulseless electric activity (with defibrillation time <2 mins), baseline "normal" neurologic status, place of cardiac arrest in monitored unit, short duration of resuscitation, absence of mechanical ventilation, absence of renal failure or hepatic failure or sepsis or malignancy or hypotension prior to arrest. This bed-side predictive tool was found to be a robust predictor of stable neurologic recovery following cardiac arrest allowing accurate prognostication in the hospital setting.

NON-ALCOHOLIC FATTY LIVER DISEASE: THE NEW RULES ARE HERE

Chalasani et al, *Gastroenterology*, 2012, outline new practice guidelines for NAFLD based on a collaboration between AGA (American Gastroenterological Association), ACG (American College of Gastroenterology) and AASLD (American Association for the Study of Liver Diseases). Amongst its 45 key recommendations are the following: diagnosis of NAFLD excludes any significant intake of alcohol, defined as more than 21 drinks per week in men or 14 drinks per week in women; other causes of liver steatoses must be considered as well as other comorbid liver disease in evaluating NAFLD, with hepatitis, drug-related hepatotoxicity, Wilson's disease, hemachromatosis, malnutrition and autoimmune liver disease being part of the differential diagnoses; liver biopsy is only recommended where a patient is thought to be at risk for steatohepatitis and advanced liver fibrosis or in patients with persistent hyperferritinemia/increased iron saturation (especially where such patients carry the C282Y gene) and in other patients with liver disease who require biopsy to ascertain true diagnosis; screening for NAFLD is not recommended as diagnostic tests and therapeutic options as presently available do not confer clear long-term benefits and cost-effectiveness for screening; treatment of NAFLD should include 3-5% total body weight loss (to reduce steatosis) or 10% total body weight (to improve inflammation/necrosis), pioglitazone (Actos) or vitamin E may be used in NAFLD which has progressed to NASH (though vitamin E should not be used in NASH cirrhosis or those with concurrent diabetes mellitus) but neither metformin nor ursodeoxycholic acid nor omega-3 fatty acids are to be recommended for either NAFLD or NASH (especially as metformin has no proven effect on liver histology); the role of bariatric surgery is promising but still ill-defined, and should not be offered to patients with underlying cirrhosis; patients with NASH cirrhosis should be screened for esophageal varices (GI bleeding) and hepatocellular cancer.

UTI: WHICH ANTIBIOTIC IS THE FAIREST OF THEM ALL?

Treating UTI is often like hitting a moving target: the condition is common, over-diagnosis is rife, follow-up is uncommon (or rare), and physicians tend to rely on their "favorite antibiotic", which is reflexly pulled up for service, much like Linus' security blanket in the comic strip, Peanuts. A recent study by Sanchez et al, *Antimicrob Agents Chemother*, 2012, underscores the problem of emerging E.coli resistance. Physicians from George Washington University and Providence Hospital, both in Washington, DC, reviewed antibiotic susceptibility data for E. coli isolates obtained from urine cultures amongst out-patients in the Surveillance Network Database between 2000 and 2010. Ciprofloxacin resistance increased from 3% to 17.1% over that 10-year span, Bactrim resistance from 17.9% to 24.2%, with only minimal shifts in resistance to nitrofurantoin, amoxicillin-clavulanate and ceftriaxone over that decade. The authors conclude that nitrofurantoin should be the drug of choice for UTIs in those with normal renal function, and amoxicillin-clavulanate or a third generation cephalosporin for all others. I suggest that we should all know our own local susceptibility patterns, treat UTIs appropriately for 3 days only, and stop treating asymptomatic patients with bacteriuria.

the SECOND OPINION

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FROM THE EDITOR

It's never hotter than in July, but this month does take the cake in more ways than one. First, the Supreme Court, that august bulwark of conservative consciousness and liberal afterthought, contrary to all predictions, voted (very narrowly, as has become the norm) to uphold the Affordable HealthCare Act, derisively called ObamaCare by the Republican opposition. Chief Justice John Roberts finally found his solomonic moment, buried deep within the arcane laws of federal taxation, but not the grist of public commerce. Next, the carefully articulated public facade of Penn State football imploded under the weight of Sandusky's pederasty, Joe Paterno's indifference, and the collective cynicism of a dozen or more university bureaucrats who were were supposed to be acting *in loco parentis*. Then, right here in paradise, a lonesome Colorado gunman drunk on delusions and myriad grudges, unleashes a fussilade of mayhem in a crowded theater: by the time it was all over, 12 fellow Americans lay dead or dying, assuming the grisly contortions of *rigor mortis*. But of course, seeing as politics is everything this election year, nobody dares ask the obvious: why would any citizen need so much fire-power in the first place? Over there, in cosmopolitan London, all gussied up and slightly tipsy, the world gathers for the quadrennial Olympics repast. This time, the ghosts of 11 Israeli athletes, massacred at Munich in their glorious prime, will hover in silent testimony to the outrage of extremism- and banal appeasement. Never again, my friends, never again. In Nigeria, a country of huge contradictions and codified corruption, premature death comes in many guises: not too long ago, a fully laden aircraft, packed with national talent and promise, was fatally undermined by an indifferent maintenance culture, lax governmental oversight and a serial hand-me-down relay of dated technology from the Western world.

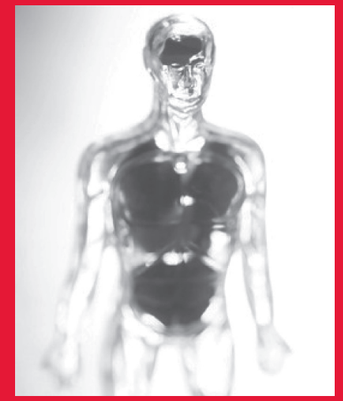
Melancholy crept unseen into my own life: my mother, an Amazon, jurist, public servant and true trail-blazer, departed this earthly life pretty much on her own terms. On quiet summer days, I can picture her traipsing the Elysian fields, or perhaps, more vividly and without complaint, accoutred in royal blue at heavensgate, solemnly teaching school. I know I will miss her, for the rest of my days. I know heaven will run more efficiently (and cheaply) with her over there.

Second Opinion will take a summer break, but shall return, *Deo Volente*, come Friday lunch-time, at our CME lounge..

Beze Adogu, MD, Ph.D, FACP

CHRONOBIOLOGY: NEW INSIGHT INTO OBESITY

Obesity has defied most modern medical interventions, and its prevalence continues to rise despite concerted efforts by parents, healthcare providers, educators, trainers and the First Lady. Obesity and related medical conditions, including type 2 diabetes mellitus, sleep apnea syndrome, NASH, atherosclerosis, presently account for a full 21% of total health care spending, estimated at $190 billion per annum. Hatori et al, *Cell Metab*, 2012, from the Salk Institute at La Jolla, provide new insight into the enigma of obesity: it is not only what you eat, but when you eat, that matters. They show that time-restricted mice allowed to eat a high-fat diet (61% of calories from fat, in contrast to "typical" 13% of fat-derived calories in normal feed) for only 8 hours daily on average ate just as much as mice that were allowed to eat ad libitum "round the clock", but were protected against obesity, fatty liver, insulin resistance or hyperinsulinemia unlike their unrestricted peers. The time-restricted mice weighed 28% less than mice which ate "round the clock" and had a higher expression of genes linked to hepatic lipolytic enzymes, suggesting that previous dogma that obesity is merely an excess intake of calories ("a calorie is a calorie" mantra) may be faulty: the body treats calories differently, depending on time of day, which in turn governs which set of genes/metabolic enzymes are turned on or off in cellular metabolism. An extension of this observation is that perhaps, during times of sleep (night-time for man, day-time for mice), there is a "braking" effect on specific metabolic pathways and nutrient utilization, and stored fat is used as a ready energy source, preventing fat accumulation and obesity. When this circadian pattern is disrupted (by artificial light, sleep deprivation, jet lag, night-time snacking, nocturnal activity, et cetera) and food is ingested at night-time, when the body is primed to use its own endogenous fuel sources, the added calories are not efficiently utilized and are consequently stored as fat, leading to obesity and related medical illnesses.



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MONOCLONAL ANTIBODIES: A NEW PARADIGM IN TREATING HYPERCHOLESTEROLEMIA

The beneficience of lipid reduction in managing arteriosclerotic vascular disease is well established, with statins now regarded as the agents of choice. Statins are able to reduce LDL cholesterol levels, but also have beneficial effects on endothelial dysfunction, anti-inflammatory properties, plaque stabilization, anti-oxidant function and enhanced nitric oxide levels, which may stimulate arterial vasodilation. However, statins, as well as other hypolipidemic agents, may not be well tolerated by individual patients. The safety and efficacy of a new monoclonal antibody directed against proprotein convertase subtilisin/kexin type 9 serine protease (PCSK9) was reported by McKenney et al, *J Am Coll Cardiol*, 2012. PCSK9 ordinarily binds to LDL receptors to reduce their numbers, and therefore, subvert intracellular LDL metabolism. As the monoclonal antibody binds (and inhibits the functional activity of) PCSK9, the internalization of LDL receptors is blocked, allowing an increase in cellular LDL receptor binding sites which in turn enhances the binding (and metabolism) of LDL cholesterol, leading to lower plasma cholesterol levels. Over a 3 month interval, monoclonal antibodies were administered subcutaneously q 2 weeks at a dose of 50 mg, 100 mg or 150 mg, or q 4 weeks at a dose of 200 mg or 300 mg. Percentage reduction in LDL cholesterol ranged from 30.5% to 72.4%, representing the most effective unit drop in LDL cholesterol with currently available medical therapy.

SUICIDE RISK IN ELDERLY: RECOGNIZING THE RISK FACTORS

Suicide is not uncommon: it is the 10th leading cause of death, with a prevalence of 11.9 events per 100,000 people. Those numbers are higher in the elderly, with 1 retiree completing the arc of suicide every 97 minutes in the United States. Anu Mehra et al, *Clin Geriatrics*, 2012, provide us with a timely reminder of the risk factors for completed suicide amongst the elderly population: Social Factors (recent life change, such as job loss or suspension of driving lisense; social isolation; bereavement; access to firearms), Demographic Factors (advanced age, rural domicile, male gender, Caucasian race), Biological Factors (age-associated conditions such as falls, arthritis, impaired mobility; environmental factors such as climate, season), Medical Factors (including chronic pain, sleep disorders/ insomnia, functional deterioration, polypharmacy), Psychiatric Factors (including cognitive impairment, major depression, bipolar disease), Psychological Factors (such as personality diusorders, coping issues, substance abuse, alcoholism), and Historical Factors (including presence of suicidal ideation, history of parasuicidal gesture, family history of completed suicide).

PREDICTING SUCCESS WITH FLUID RESTRICTION IN HYPONATREMIA

Hyponatremia is the most common electrolyte abnormality and is associated with increased morbidity/mortality, longer hospitalization and a higher incidence of ICU care amongst hospitalized patients. In chronic and mild/moderate hyponatremia, fluid restriction is often advanced as the safest and cheapest form of management, though long-term studies clearly demonstrate that this regime only provides modest improvement in serum sodium levels, has a slow onset of action (often taking days to provide therapeutic benefit), and is intolerable for most patients due to associated symptoms of thirst and clinical dehydration. Proper fluid restriction limits all IV and orally ingested fluids, and daily intake should be targeted to [24 hour urine output - 500] mL only. The following findings suggest that fluid restriction will be unsuccessful, therefore indicating a switch to vaptan therapy:

1. Less than 2 mmol rise in serum Na in 24 hours of aggressive fluid restriction (especially if intake <500 mL/day).
2. High urine osmolalilty >500 mOsm/kg.
3. Presence of oliguria or total urine volume under 1250 mL/day.
4. [Urine Na + Urine K] > Serum Na.
5. Clinical findings indicative of either water/fluid deficit or hypovolemia or severe dehydration.

COMPLICATIONS OF CHRONIC THERAPY WITH PROTON PUMP INHIBITORS

PPIs are useful for treating several gastrointestinal conditions associated with gastric hyperacidity or pathologic hypersecretory status. Currently, PPIs are the #3 most commonly prescribed medications in the United States, with most patients being on "indefinite" therapy. A short article by Ament et al, Am Fam Physician, 2012, reviews the complications associated with long-term acid blockade:

1. High risk of hip fracture in the elderly and others at higher risk for osteoporotic fractures (CKD, chronic steroid therapy, prolonged immobility, history of diabetes mellitus).
2. Inhibition of cytochrome P450 2C19 isozyme (which activates Plavix) thereby blocking the therapeutic effects of Plavix and similar anti-platelet drugs, and thus increasing re-infarct rates in CAD; therefore, for CAD patients at high risk of recurrent GI bleeding based on prior GI history, concurrent therapy with ASA/ steroids, advanced age, stage IV/V CKD, co-infection with H. pylori or concurrent Coumadin use, gastroprotection should best be attained with either H2-blockers or sucralfate, or possibly, Protonix.
3. High gastric pH from chronic proton blockage reduces iron absorption resulting in long-term iron deficiency.
4. Higher risk of secondary bacterial infections: C. difficile enteritis (in patients on both PPIs and antibiotics), Campylobacter/viral gastroenteritis, community-acquired pneumonia.
5. Tendency to rebound hyperacidity on PPI withdrawal with recrudescence of gastrointestinal symptoms.

DROTRECOGIN: THE WONDER DRUG ATTEMPTS RESURRECTION

Drotrecogin alpha (activated), a.k.a. Xigris, recombinant human activated protein C, has been proposed for treatment of severe sepsis based on early reports that suggested a reduction in mortality amongst septic shock patients by ~20%. Despite the considerable risk associated with its use (which includes potentially life-threatening bleeding), it was originally approved by the FDA in a split 10:10 decision for hospital use. Since then, Marco Ranier et al, *N Engl J Med*, 2012, report findings from a randomized, double-blind, placebo-controlled, multi-center trial which assigned 1697 patients in septic shock to receive either Xigris at 24 mcg/kg weight/hour or placebo for 96 hours. Primary outcome was assessed as death from any cause within 28 days of randomization. At 28 days, 26.4% of Xigris-treated patients and 24.2% of placebo-treated patients had died, rising to 34.1% in Xigris group and 32.7% in placebo group at 90 days. In a sub-study, patients with severe protein C deficiency at baseline had a mortality of 28.7% with Xigris at 28 days and 30.8% with placebo at 28 days. The inescapable conclusion was that Xigris did not reduce mortality in sepsis. Now, comes a meta-analyses and meta-regression study from Kalil & LaRosa, Lancet Infect Dis, 2012, studying the effectiveness of Xigris over the past 10 years and matching those findings to the original PROWESS trial which put Xigris on the ICU map in the first place. They used 9 controlled trials (41,401 patients) and 16 single-group studies (5,822 patients) as well as an additional 20 studies (8,245 patients) added for safety analyses. They found a 18% reduction in hospital mortality with Xigris, a figure similar but not identical to the PROWESS result, but serious bleeding was found in 5.6% of patients which was significantly higher than the quoted 3.5% from PROWESS.

VASCULITIC NEUTROPENIA: CONSIDER LEVAMISOLE IN DRUG USERS

Cocaine addiction is a common affliction, with over 5 million Americans regularly smoking/inhaling, snorting or injection cocaine or its metabolites. Severe neutropenia has been reported amongst cocaine addicts which has now been linked to drug "cutting" with levamisole, a synthetic imidazothiazide antihelminthic with notable immuno-modulatory properties, previously utilized as "steroid sparing therapy" in childhood nephrotic syndrome, disease-modifying agent in rheumatoid arthritis, and adjuvant (to 5-FU) in colon cancer treatment. Clinical manifestations of levamisole poisoning are: painful hemorrhagic bullae on head/ neck, large joint arthralgias with fatigue and malaise, superficial reticulated purpura of skin, severe neutropenia, positive ANA (speckled pattern), positive ANCA profiles, seizures, lung hemorrhage, pauci-immune glomerulonephritis, and perhaps, most diagnostically relevant, positive anti-human elastase antibody (Kachiu Lee et al, *Mayo Clin Proc*, 2012).

IMPROVED RENAL FUNCTION WITH STATINS: WHERE IS THE DATA?

Pleiotropic effects of statin drugs, those manifestations which are not readily explained by their ability to block HMG CoA reductase, are legion. The concurrence of cardiac and renal dysfunction which is often described as "cardio-renal syndrome" is common, conferring worsened prognosis on both CKD and CHF patients. A post-hoc analysis of the TNT trial (Treating to New Targets) by Jennifer Ho et al, *Am J Cardiol*, 2012, studied the decrease in heart failure hospitalizations associated with long-term statin use in cardiac patients. Recruiting 10,001 study participants, eGFR was assessed at baseline and again at 1 year in 9,376 of those patients placed on either 10 mg vs 80 mg Lipitor daily, and Cox regression models used to evaluate the relationship between later (decreased) hospitalizations and reduction in eGFR over 1 year. Amongst patients on low-dose Lipitor, there was little change in eGFR, but a significant improvent of eGFR (1.48 mL/min) was noted in the 80 mg Lipitor cohort. On adjusting for baseline eGFR, each 5 mL/min rise in eGFR at 1 year was associated with a 15% drop in later hospitalizations whicvh was independent of LDL cholesterol level. This study suggests that high-dose statins may be beneficial in improving eGFR, which in turn helps reduce cardiac hospitalizations in patients with cardio-renal syndrome, irrespective of specific effects on LDL cholesterol levels.

CANCER VULNERABILITY: GLYCINE DEPENDENT METABOLIC PATHWAYS

Uninhibited and uncontrolled cellular proliferation is the hallmark of cancer. Cancer treatment is sensibly directed towards controlling cellular growth, but so far, cancer cells show few, if any, metabolic vulnerabilities. Mohit Jain et al, *Science*, 2012, report that rapidly growing cancer cells show a specific requirement for glycine-dependent metabolic pathways, a feature that is absent in rapidly growing non-cancerous cells, and may betray a potent vulnerability within neoplastic cells. Using CORE profiling, a technique that measures metabolic fluxes and time-dependent changes in amounts of individual chemicals consumed and released as part of intermediary cell metabolism, a panel of 60 well-characterized neoplastic cell lines (NCI-60), were systematically studied. Glycine consumption was found to relate highly to speed of cell division in cancer cells, whilst slowly dividing cells (presumably in quiescence) released rather than consumed glycine. Their findings were corroborated by measuring the expression of nearly 1500 metabolic enzymes, where again, enzymes responsible for intra-mitochondrial glycine biosynthesis correlated with rapid cell growth. When glycine was removed from the cell culture medium or glycine-dependent enzyme pathways blocked, rapid cancer cell growth was abolished. As cell culture results do not necessarily correlate with findings at the organism level, it was reassuring that the researchers found that high levels of expression of enzymes involved in glycine metabolism correlated with poor outcomes in breast cancer patients. Finally, are we approaching a new paradigm for cancer vulnerability- or will it go the way of intracellular tetracycline accumulation, once thought to be the Achilles' heel for neoplastic cellular targeting?

MORTALITY IN ATRIAL FIBRILLATION: RATE VS RHYTHM CONTROL

As the population ages, the prevalence of atrial fibrillation will surely rise, as would its multivariate complications and co-morbidities. Despite the wealth of research into this condition, treatment is far from uniform, employing diverse modalities in variable combinations which include: anti-coagulation, anti-arrhythmic drugs, foci ablation, ventricular rate control and electrical cardioversion, often in unpredictable (and idiosyncratic) ways. Ionescu-Ittu et al, *Arch Intern Med*, 2012, used a population-based administrative database from Quebec, Canada, to select patients >65 y.o. diagnosed and hospitalized with atrial fibrillation between 1999 and 2007. A total of 26,130 patients were identified and followed for a mean period of 3.1 years (until death or administrative censoring). In the first 6 months, there was a small increase in mortality for patients treated with rhythm control vs. those treated with rate control; thereafter, mortal;ity was similar amongst both groups until year 4, then mortality began to steadily decrease in rhythm control group from year 5.

ATRIAL FIBRILLATION IN OLDER WOMEN ASSOCIATED WITH HIGHER STROKE RISK REGARDLESS OF COUMADIN USE

Atrial fibrillation is a serious and common cardiac rhythm disorder, accounting for a third of all hospitalizations for cardiac arrhythmias, and afflicting 2.2 million persons in the United States, manifesting as either persistent or paroxysmal disease. Stroke is a frequent complication amongst older patients, with strokes being 5x more common in atrial fibrillation than in the general population, and associated with female gender, advanced age and a previous history of stroke(s). Annualized stroke rate is estimated at 1.6% in males and 3% in females, a female preponderance replicated in several historical trials such as Framingham Heart Study, ATRIA and SPAF studies. The assumption was that the female excess in stroke rates might be related to under-utilization or under-prescription of coumadin, itself a controversial subject which has been supported by some, but not all previous studies. Tsadok et al, *JAMA*, 2012, set out to measure stroke risk in a population-based cohort study of 39,398 males and 44,115 females >65 years old who had been diagnosed with atrial fibrillation between 1998 and 2007. At admission to the study, females generally had a higher stroke risk as estimated by the predictive CHADS2 score (congestive heart failure, hypertension, age >75 y.o., diabetes mellitus, prior stroke/TIA, female sex: for those with CHADS2 score <2, a more sophisticated risk profile incorporates age >65 and vascular disease in the CHA2DS2-VASc point score system); at conclusion, though men often started out with a higher dose of coumadin (which itself was meaningless, in the absence of supportive INR data that higher doses actually translated to improved anticoagulation) but were actually more likely to fill and use their coumadin prescriptions than men. The difference in stroke rates between the sexes was confirmed by multivariable Cox regression analysis, which showed a persistent female preponderance even after adjusting for baseline comorbidities, individual components of the CHADS2 score system and coumadin treatment. The researchers conclude that the female excess in stroke rates was primarily driven by the excess in event rates recorded amongst the >75 y.o. cohort and could not be explained by differential coumadin use.

TRADITIONAL AND NOVEL RISK FACTORS FOR PAD IN CKD PATIENTS

Peripheral artery disease is common in CKD patients. Chen et al, *Am J Cardiol*, 2012, set out to examine the cross-sectional association between novel risk factors for PAD in the chronic kidney disease population. A total of 3758 patients were recruited from the CRIC cohort, and prevalent PAD defined as ankle-brachial index <0.9 or a past history of arm/leg revascularization. Traditional risk factors of advanced age, cigarette smoking, physical inactivity, chronic arterial hypertension, diabetes mellitus, hyperlipidemia, pulse pressure were accounted for and adjusted. Several novel PAD risk factors were uncovered: hsC-reactive peptide, WBC count, fibrinogen level, hyperuricemia, elevated hemoglobinA1c, high cystatin C and insulin resistance index. They conclude that prothrombotic status, oxidative stress, inflammation, insulin resistance and cystatin C were powerful predictors of PAD amongst CKD patients. Further studies to determine causality would help define the impact of these novel risk factors.

MSSA: BLAME THE RESIDENT DOC, NOT PATIENTS

Schwarzkopf et al, *J Bone Joint Surg Am*, 2012, from New York University Hospital for Joint Diseases report a higher prevalence of methicillin-sensitive Staph aureus among trainee orthopedic surgeons when compared to a group of high-risk surgical patients. Nasal swab cultures from 74 attending orthopedic surgeons and 61 residents were screened for both MRSA and MSSA and the results compared to a prospective database of nasal cultures retrieved from those undergoing joint replacement and spinal procedures. There was no significant difference in the prevalence of MSSA infections between physicians (1.5%) and patients (2.17%) but MSSA colonization was significantly higher among physicians (35.7%) compared to patients (18%), the difference being primarily attributed to a higher rate of MSSA colonization among residents (59%), whereas it was only 23.3% among attending surgical staff. The authors conclude that residency training status or activities integral to training might predispose to MSSA colonization. It remains unclear if routine decolonization will help reduce the risk of post-surgical wound infections in orthopedic.