Healthcare Associated Infections

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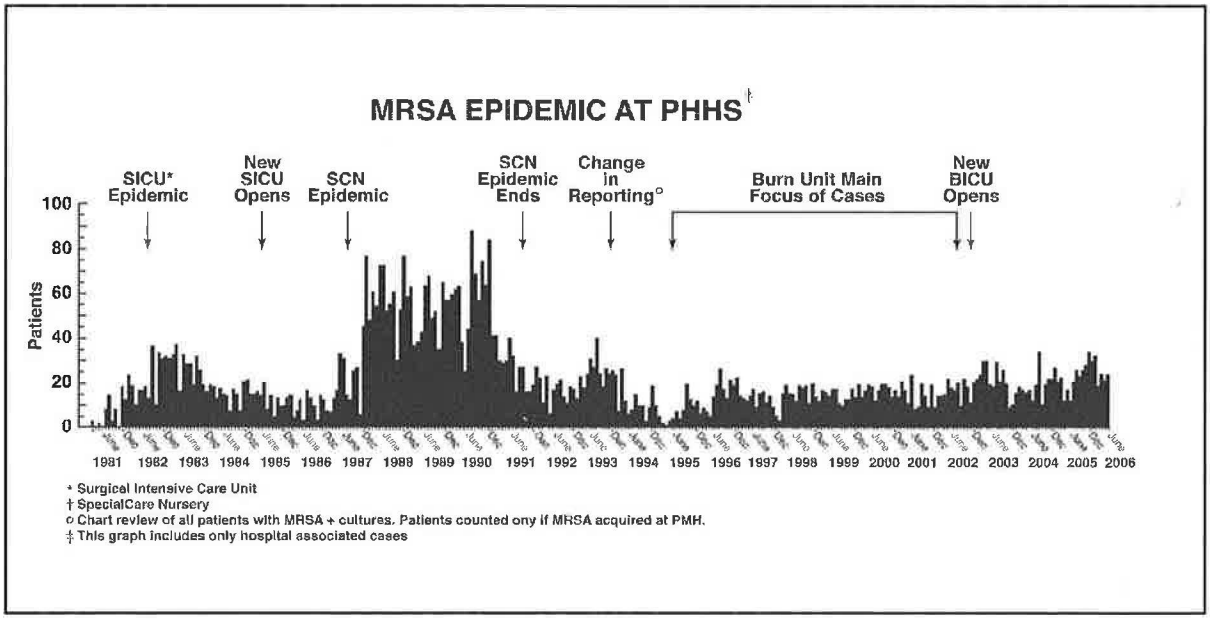
Methicillin-resistant Staphylococcus aureua (MRSA)

Methicillin-resistant Staphylococcus aureua (MRSA) became a significant problem in the United States in the late 1970's. Parkland Memorial Hospital had its first case in 1981 and shortly thereafter an epidemic in the Surgical Intensive Care Unit (SICU) occurred. This was in the old SICU where the beds were crowded together and there was little space between patients. During the most intense phases of the epidemic, all patients became colonized within 48 hours after admission into the SICU. Figure 1 shows the number of hospital acquired MRSA cases by



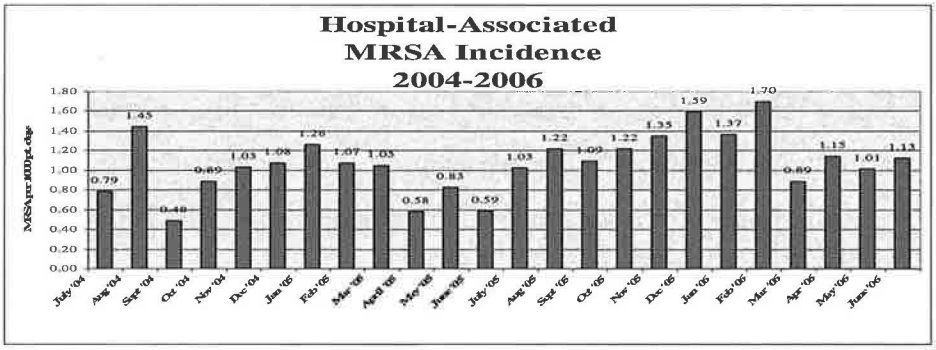
Month from 1980 through 2006. While there was some control of the MRSA in the SICU with conventionalized isolation procedures, the solution to the epidemic was the opening of a new SICU in the newly constructed building. There was adequate space between patients in the new SICU and subsequent cases have usually been sporadic and isolated. A new epidemic began in 1987 and continued through 1991 and centered in the Special Care Nursery (SCN) and the Neonatal Intensive Care Unit (NNICU). Around 1992 a change in reporting occurred to reflect the fact that cases were having their inception in other healthcare institutions. In about 1998 community acquired (CAMRSA) began to become more of a problem. During that year, 3 cases of CAMRSA bacteremia were hospitalized. The Burn Intensive Care Unit (BICU) was the major focus of MRSA cases at Parkland from 1995-2002. This epidemic receded after the opening of the new BICU in 2002. HAMRSA cases are denoted as such only if they have

acquired MRSA during their stay at the hospital with the first evidence of infection or the first cultures indicating colonization occurring 48 hours or longer after hospitalization. Community acquired MRSA represents an increasing problem particularly since 2000. Patients with CAMRSA acquire colonization or disease while in the community. They can be admitted to the hospital. These cases still give rise to other cases of MRSA in the hospital which are then considered to be healthcare associated (HAMRSA). There is interplay between HAMRSA and CAMRSA. Cases of CAMRSA can be admitted in the hospital and have given rise to small epidemics which are especially noticeable in a setting like the NNICU.

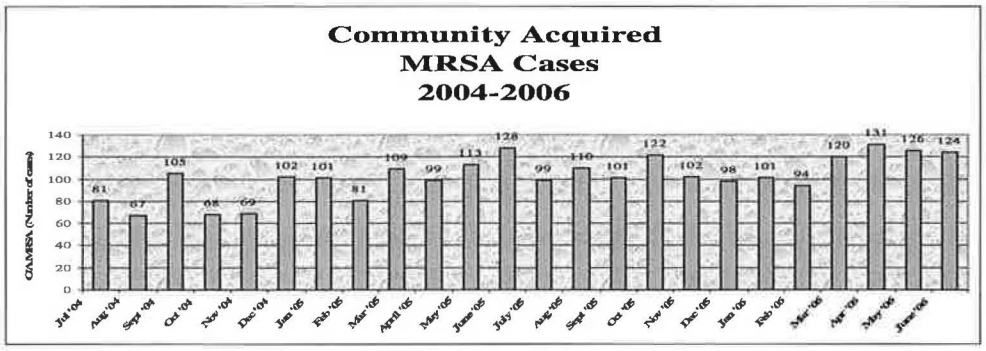
Although CAMRSA can give rise to cases of HAMRSA, in general, the 2 categories of cases are usually separable and distinct and can be further defined by certain characteristics. HAMRSA organisms have different PFGE types and have Staphylococcal Chromosome Cassette (SCC) mec A gene types 1-3 and they usually do not have Panton-Valentine Leukocidin (PVL) toxin. CAMRSA first began to be recognized as a significant problem around 2000. Their PFGE types belong to a large family and are clustered under the designation of USA clone 300. The SCC mec A gene is type 4, and they commonly possess a gene coding for PVL toxin. HAMRSA strains usually have susceptibility only to vancomycin whereas CAMRSA strains have less DNA coding for resistance genes and are susceptible to multiple antibiotics including vancomycin but also to other antibiotics like sulfatrimethoprim, tetracycline, rifampin, and clindamycin,. Particular patients that are predisposed to become colonized with hospital acquired strains include hospitalized patients, aged persons, burn patients, dialysis patients, and patients in intensive care units. The disease states that these organisms produce are burn wound infections, surgical site infections, central line associated blood stream infections (CLA-BSI), surgical site infections (SSI), ventilator associated pneumonias (VAP), and urinary tract infections (UTI). HAMRSA strains are poorly transmissible in the community. In contrast, community acquired strains are readily transmissible in the community and affect apparently normal persons including children, athletes, men having sex with men, prisoners in jail, patients with diabetes, intravenous drug users and commercial sex workers. Although these strains mostly produce skin and soft tissue infections (SSTI) and often require nothing but incision and drainage for therapy, they are also capable of producing necrotizing pneumonia with and without preceding influenza and by cases of purpura fulminans. Using total cases of HAMRSA for PMH in 2006, the bacteremia rate in the year 2006 for hospital acquired strains is 9.4%. For patients

on Medicine the bacteremia rate was17.6%. Community strains produced a 3.3% bacteremia rate if all cases of CAMRSA seen at PHHS is used as a denominator. This bacteremia rate is not so much a measure of intrinsic virulence as it is a reflection of host status colonized with a particular strain.

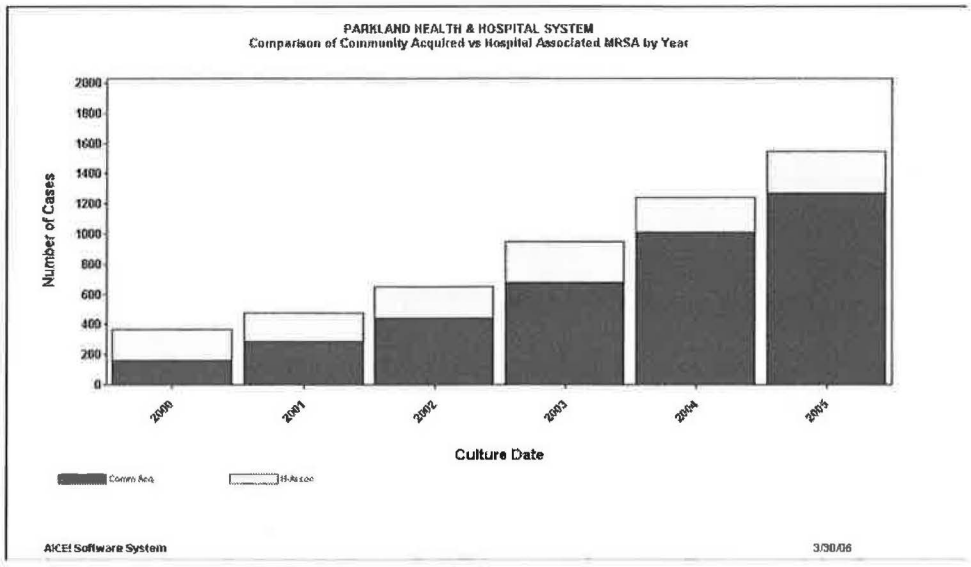
The transmission of MRSA is usually by contact. Patients are colonized and then the hands of personnel handling these patients carry the organisms to other patients. It is infrequent for personnel to become permanently colonized with HAMRSA strains. To control this contact transmission, patients are identified and placed in isolation. In an infrequent mode of transfer of HAMRSA, the use of the same device between patients has been shown. The basic transmission cycle of HAMRSA usually is independent of environmental MRSA. Aerosol dissemination is rare and limited to special patient situations. Transmission is limited by prophylaxis including triple dye and mupirocin. Usually control is by isolation, improved staffing ratios, cohorting and other maneuvers. HAMRSA incidence is depicted in Figure 2 for the years 2004 to 2006 for



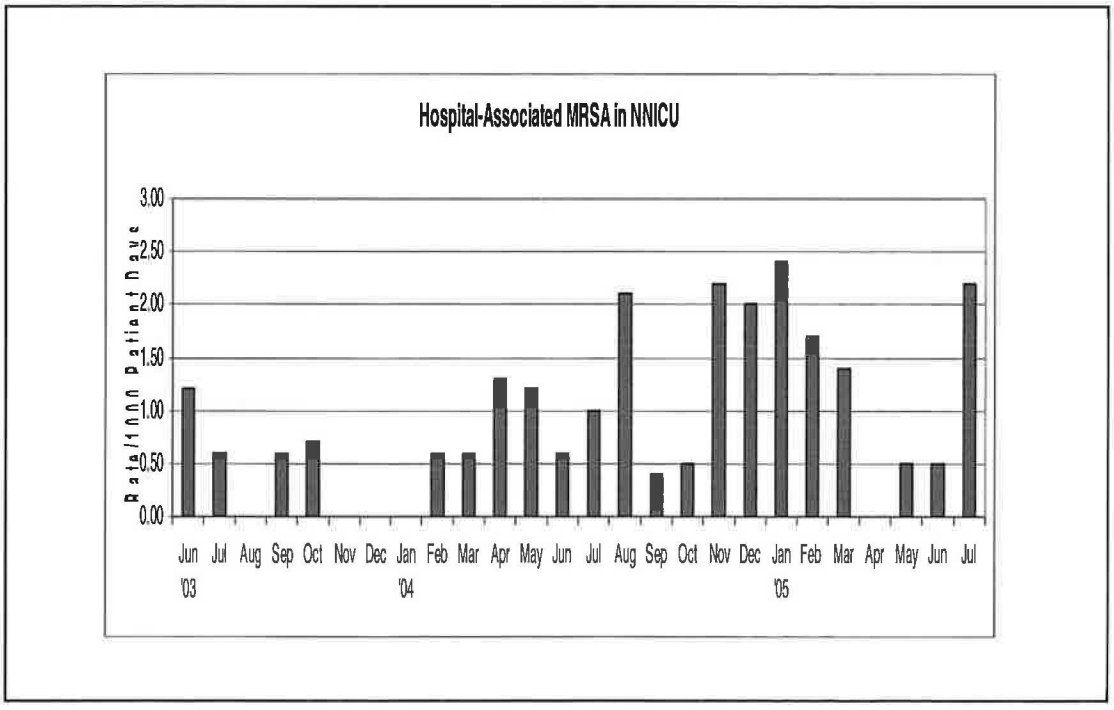
PHHS. The number of cases per 1000 patient days per month is shown with variation by month with no consistent trend apparent CAMRSA cases are increasing as shown in Figure 3,



but these cases are usually seen in the outpatient clinic setting or in the Emergency Department. Healthcare associated cases of MRSA since 2000 are relatively stable in number but community acquired cases seen at PHHS have progressively increased in number (Figure 4).

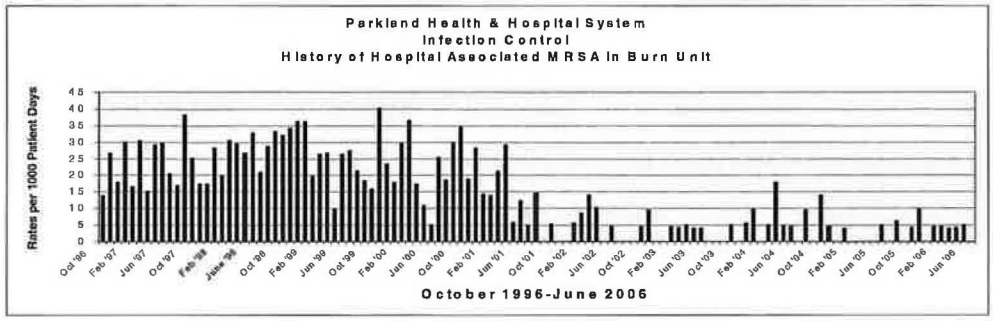


The special care nursery MRSA epidemic was valuable as a major teaching experience. From 1987 to1991, 40-60% of infants discharged from the special care nursery (>1000 infants) were colonized with one PFGE type MRSA strain. However, this PFGE type despite its constant introduction into the community never became established as a community strain. MRSA was a major SCN pathogen and in infants with disease, the case-fatality rate was 19%. Ending the epidemic during its peak was thought to be impossible. However in 1991, there was an important interplay of factors which eventually eliminated the epidemic. These factors were 1) an improved staff/patient ratio. 2.) A new Infection Control nurse was delegated to spend all her time working with the problem. She empowered the staff to believe that they could control the epidemic. She better identified colonized infants and made that status known and kept the staff informed about the progress in controlling the epidemic. 3.) Single devices were utilized to facilitate eye examinations of infants where before, one device was used between multiple infants. A disposable instrument now was used for each infant. 4.) It was thought that triple dye was contraindicated in low birth weight infants because of possible systemic absorption from skin. However, after umbilical vein cord catheterization, triple dye was applied to the umbilical cords of infants and proved a major factor in delaying colonization with MRSA. 5.) Finally, with a decreased number of infants that were colonized or infected, patients were cohorted. After the epidemic, there were infrequent introductions of MRSA into the SCN with multiple PFGE types and the nursery remained largely free of MRSA. The situation has changed now so that mothers enter the hospital, colonized with CAMRSA and these strains are being introduced more frequently into the SCN with a potential problem of spread between infants (Figure 5).



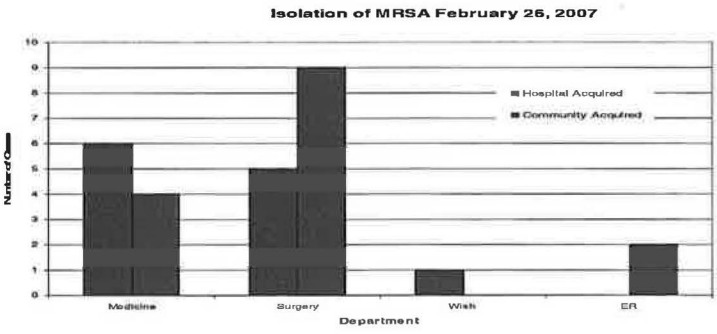
The BICU epidemic was a major problem from 1995 through 2002 and was the major source of HAMRSA in the hospital. During peak episodes, everybody in the BICU and most people in its step-down unit, the Burn Acute Care Unit (BACU) were colonized with MRSA. During intense transmission periods all patients in the BICU became colonized in less than 72 hours. It was a major pathogen within the BICU. Patients without burns but with other conditions requiring ICU placement namely, trauma or medical patients, infrequently became colonized. Just 2 PFGE MRSA types circulated. Despite the fact that all burn patients on admission were cultured and isolated and kept in isolation until discharge did not eliminate the transmission of MRSA in the Burn Unit. It was reasoned that other factors must have been operative in facilitating transmission within this unit. Measurements were made which indicated that in control patients in ICU settings, MRSA was never significantly aerosolized into the room. The room space for each patient in the BICU was limited and built in accordance to 1985 recommendations. The rooms were sufficiently small that doors could not be closed during dressing changes. Using a Burkhard air sampler, 2 rooms of burn patients undergoing dressing changes were tested to determine whether aerosolization of MRSA occurred during burn dressing changes. In each instance organisms were found by the air sampler. Furthermore, air sampling outside the rooms also demonstrated the presence of aerosolized MRSA during the dressing changes. In one instance, aerosolized MRSA, was found before the dressing changes. It was thought possible that with open doors during dressing changes, MRSA was aerosolized and potentially could have infected other patients in nearby rooms.

The PMH Burn Unit is a regional burn center and is noted for excellence. The American Burn Association (ABA) regularly visits and inspects burn units across country. They thought the PMH BICU problem was distinctly unusual because of its persistence and intensity and the hospital was urged to devote as much attention as possible to eliminate or control the problem. All these factors were considered by the surgeons in charge of the Burn Unit, by the Infection Control Committee, by Nursing and by the Administration. With donor support it was decided to build a new BICU; the room space was greatly increased per patient and the number of rooms was decreased from 12 to 9. The rate of MRSA colonization and/or infection fell with building of BICU (Figure 6).



From 1996 thru 2001the mean case rate was 21.9 per 1000 patient days but after patients had been moved into the new Burn Unit from 2003-Sept. 2006 the mean case rate was 3.4. The difference in case rates between periods had a z test value of 11.5, $p<0.0001$. The new BICU now infrequently has cases of MRSA and they are of different PFGE types. The older 2 resident PFGE types have disappeared. New MRSA cases in the BICU are usually transferred from the community were they represent CAMRSA strains.

The new problem of MRSA at PMH revolves around simply the fact that we continue to transmit MRSA on the Wards both in Medicine and Surgery and this is being added to by the number of people with CAMRSA admitted into the hospital. Figure 7



shows a typical day in the terms of the number of patients who are isolated at any given period at Parkland. Patients in Surgery are more numerous than patients in Medicine. On Surgery, MRSA is a major cause of surgical site infections and central line associated blood stream infections. In 2006, 319 patients developed MRSA colonization or infection at the hospital. One hundred nineteen of these patients were on Medicine; 28 of the 119 (23.5%) were colonized, 91 of the 119 (76.5%) had infection or disease. Of the 119 patients on Medicine, 21 (17.6%) developed or had positive blood cultures. In 2 surveys of patients under contact isolation precautions, less than 5% were eligible to determine whether their nasal colonization status had disappeared. The natural history of patients who have HAMRSA colonization or infection is not known. Some patients spontaneously lose their colonization status. At Parkland about 50% of patients spontaneously lose colonization. In patients studied at 16 intensive care units across the country about 70% of patients spontaneously lost their MRSA colonization status an observation period of one year. Decolonization protocols have been used with varying degrees of efficacy, but in one recent study of a 7 day course of chlorhexidene baths, mupirocin ointment to the anterior nasal vestibule and rifampin with doxocycline led to a decrease was in colonization that was highly statically significant. Patients were followed by cultures from the anterior nares, the perianal area, skin lesions, catheter exist sites, and previous positive culture sites were sampled to assess colonization loss.

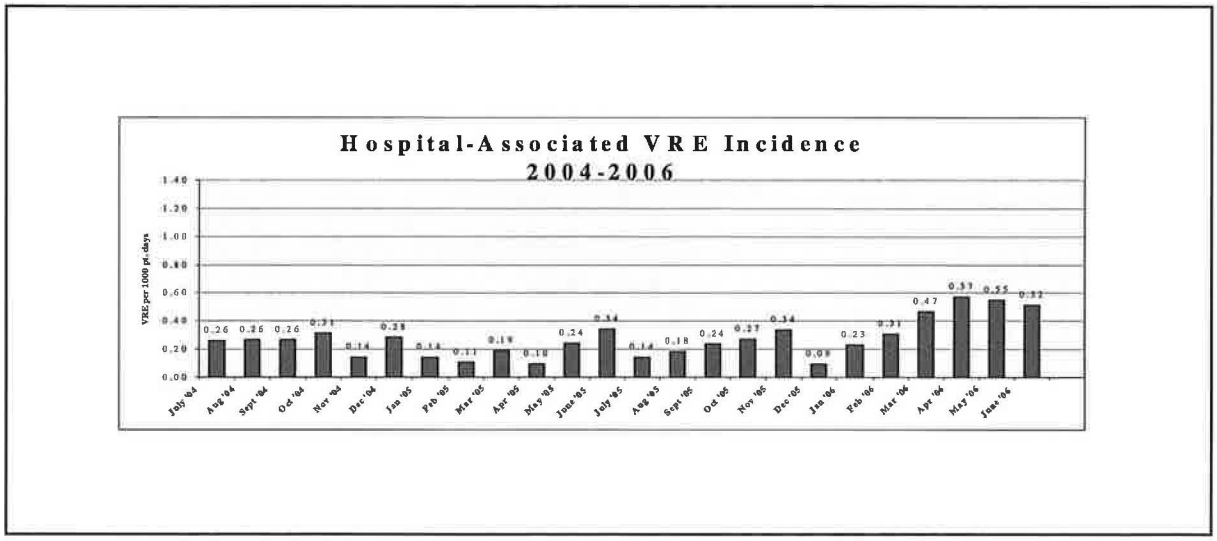
We have major problems with regard to HAMRSA. There are areas in the hospital that have patient population particularly predisposed to MRSA, namely the BICU, the Special Care Nursery, and Intensive Care Units. These patients often are on ventilators and have central lines. Programs must be in effect to control the spread of this organism within the hospital. Now it is not practically possible to distinguish HAMRSA from CAMRSA. It is important to identify patients who have spontaneously lost MRSA colonization so they do not have to be isolated on readmission. Certain hospitals have utilized PCR methodology to detect MRSA rapidly upon readmission back into the hospital. It may be possible on a study basis to decolonize selected patients intentionally. A meta-analysis has revealed that 4 out of 6 studies that were properly controlled demonstrated a positive effect of isolation in diminishing hospital spread of MRSA although in two studies there was no such effect. As the stories of the MRSA epidemics at PMH illustrate, new innovative ideas are to control this pathogen urgently needed.

Vancomycin Resistant Enterococci (VRE)

Vancomycin Resistant Enterococci have become widely spread particularly in certain institutions. In Europe, use of the antibiotic, avoparcin, in livestock led to resistance in Enterococci which then spread to humans. In the U.S., this selective pressure was not present, but wide spread antibiotic usage patterns in patients was a predisposing factor. There was wide-spread use of vancomycin and third generation cephalosporins. Enterococci are not a highly virulent pathogen but they can become highly prevalent in hospitals. If infection control is not practiced, the VRE prevalence on a general medical ward may exceed 35%. Vancomycin resistant genes in VRE are capable of being passed to MRSA and producing VISA and VRSA. Some VRE disease states are presently not treatable with antibiotics and these include endocarditis and meningitis.

In a bone marrow transplant center in a hospital on the East Coast, Enterococci were described that required the presence of vancomycin for growth and replication, vancomycin dependent Enterococci. This represents an extreme, but illustrative example of antibiotic use and selective pressure inducing an increased prevalence of the organism. The epidemiology of VRE and its isolation necessitate knowledge of the fact that the colonized patient can contaminate the environment and that contact can result in colonizing the hands and the clothing of personnel entering the room and touching the patient. Rectal thermometers, bed surfaces, telephones, other items can become contaminated; by handling these, personnel can spread the organism to other patients. Patients become colonized for extended periods and there are no established effective decolonization protocols. To detect unrecognized cases that may cluster about an infected patient active surveillance culturing is necessary. After discharge terminal cleaning of the room is mandatory to remove environmental VRE and prevent colonization of a new patient entering the room.

With knowledge of the problems that East Coast hospitals were having with VRE, there were concerted efforts made to keep the prevalence of this organism at a low level in other hospitals in the U.S. that were not involved during the early part of the epidemic. At PMH, hospital associated VRE incidence and prevalence is at a low grade and usually only between 2 and 5 hospitalized patients are colonized at any time (Figure 8).

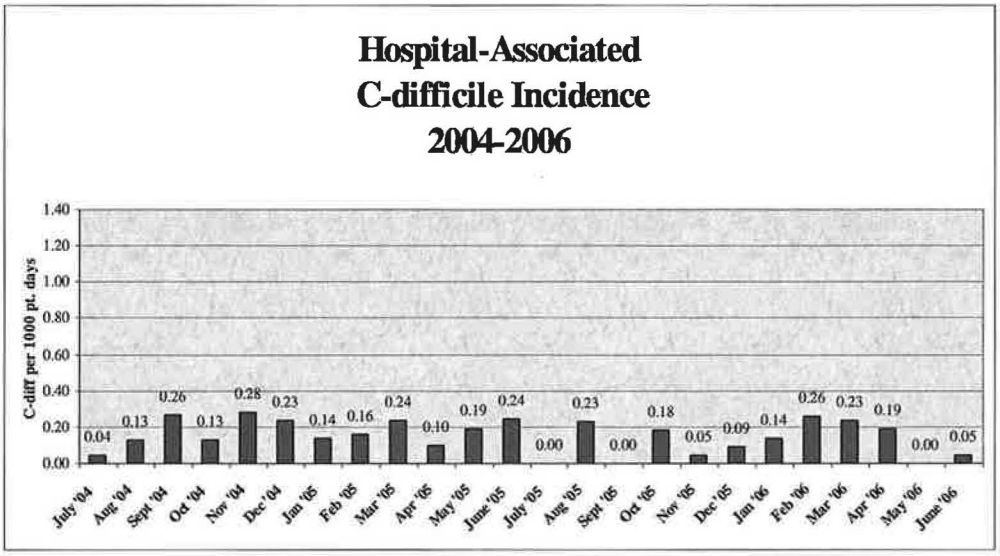


Although there are no established effective decolonization protocols, there is some spontaneous loss of carriage and it may be possible by culturing patient after a period to remove some from having to be isolated again on readmission to the hospital. A recent study involving multiple intensive care units demonstrated that as many of 80% of persons colonized had lost gastrointestinal carriage during a year follow-up.

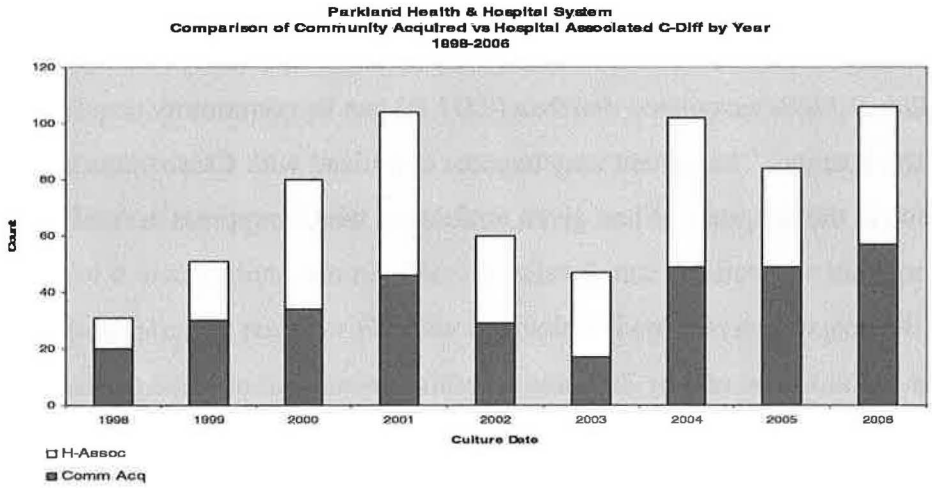
Antibiotics for serious illness due to hospital associated MRSA and VRE include vancomycin, synercid, linezolid, daptomycin and tigecycline. Vancomycin cannot be used for VRE and other antibiotics like daptomycin and tigecycline are not recommended. Synercid and linezolid can be used for VRE but these are toxic drugs and are only bacteriostatic against VRE.

Clostridium Difficile Associated Diarrhea (CDAD)

Clostridium Difficile associated diarrhea (CDAD) can be community acquired, but it is often acquired in the hospital. The patient may become colonized with *Clostridium difficile* during their residence in the hospital. When given antibiotics which suppress normal intestinal flora, *C. Difficile* overgrows and patients can develop disease. In one study, about 6 to 7% of patient admitted to the hospital were already colonized with *Clostridium difficile*. Hospitalization increased the colonization rate by 20% and a certain percentage of these patients developed diarrhea. Cases of CDAD often cluster in time and place on wards of the hospital. Figures 9



and 10 show the rates of CDAD as cases/1000 patient days by month at Parkland and the ratio of community to hospital associated cases by year (Figure 10).



Of critical importance is the recognition of a new hyper- virulent strain of *C. difficile*. This strain has become most prominently clinically manifest in Quebec, Canada and in the northeastern United States including Boston, New York and Pittsburg. This new strain has a restriction endonuclease analysis (REA) grouping of group B1. It has a PFGE type designated as NAP 1. It is toxinotype III and it is positive for the binary toxin CDT. These strains contain an 18–bp tcdC deletion. This deletion allows the strain to produce 16 to 23 times more of toxins A and B in vitro. These strains are marked by fluoroquinolone resistance and in certain hospitals selection by fluoroquinolone use. Once infected, the disease is more frequent in elderly persons and the case-fatality rate can approximate 7 to 17%. Fulminant cases can be seen. Leukemoid reactions, toxic megacolon, shock, protein loosing enteropathy, and requirement of colectomy for survival characterize the disease.

Patients with CDAD are isolated in a similar fashion to VRE patients and spores of *C. difficile* soil the environment. Beds, bedding, the floor, commodes and bed pans become contaminated. The patient is infectious as is his environment. The environment may remain contaminated for long periods of time unless properly cleaned. Patients should generally be isolated for the remainder of their hospital stay. If the hospitalization period is long and diarrhea has ceased, the patient can be removed from isolation if the rooms and the equipment are properly cleaned. To remove spores, terminal cleaning should include a step where a 1:10 dilution of bleach is used. To isolate these patients, gowning and gloving is necessary. Hand-washing requires the use of soap because alcohol degermers alone have not effect on spores. If disease rates in the hospital do not decline, the returning patient must be considered infectious until negative stool toxin tests are available. Therapy of CDAD is either oral metronidazole or vancomycin. If the disease is severe, vancomycin as initial therapy is preferred over metronidazole. IV metronidazole can be used in conjunction with oral vancomycin in sicker patients. Local administration of antibiotics may be necessary either by nasogastric tube, cecostomy or retention enemas. In certain patients, IVIG should be a considered for use. For the new strain of *C. difficile,* colectomy with a high case-fatality rate may be necessary for survival. Recurrences are common and the antibiotic course must be repeated or else a tapering dose or pulsed doses of antibiotics are necessary.

Acinetobacter- an ICU Pathogen

There are multiple *Acinetobacter* species, the most important of which are *Acinetobacter baumanii* and *Acinetobacter Calcoaceticus*. The organisms are usually termed as *Acinetobacter* or *Acinetobacter baumanii-Calcoaceticus* complex. To illustrate the *Acinetobacter baumanii* problem, an outbreak in the Parkland Memorial Hospital MICU will be described. During April - May 2003, *A. Baumanii* was isolated from patients in the MICU. In total over the 2 month period, there were 11 cases with 5 ventilator associated pneumonias, 3 urinary tract infections, 1 bacteremia and 2 deaths. To insure a complete case count, an active surveillance program was instituted by culturing respiratory secretions and urine of contact patients. All of the isolates identified in this outbreak had identical antibiotic susceptibility patterns that are they were resistant to all antibiotics except for tobramycin, amikacin, imipenem, and meropenem. At least 9 of the isolates were sent the State Health Department for PFGE typing and all isolates were identical. With recognition and control procedures, the outbreak came to an end in the MICU in May. The outbreak was deemed a "sentinel event" by the hospital and its origin was investigated in detail. It was observed that there was increased third generation cephalosporin use in the MICU in early 2003. . It was noticed that before the outbreak, that inadequate hand hygiene and isolation practices were not uncommon. It was also noted that respiratory equipment for patients was not being discarded with patient discharge from the unit and was placed in a bedside drawer where it often remained for the hospitalization period of several patients. The respiratory equipment included mostly new but also some used tubing, saline bullets, and nebulizers. It was postulated but not proven by culture that *Acinetobacter* was spread to these items and then to new equipment placed in the drawers and then back to new patients. It was observed that ventilators were not removed from the MICU promptly for cleaning when patients were discharged. After recognition of the outbreak and knowledge that these bacteria have a great propensity to become more antibiotic resistant with time, control procedures were instituted which included disseminating information about the outbreak and discussing isolation practices and hand hygiene. Colonized MICU patients were placed in contact isolation, respiratory equipment was discarded after patient discharge, and ventilators were promptly removed from the MICU after patient use. Respiratory tract cultures on ventilated patients continued to be preformed to find new cases. An Environmental Services

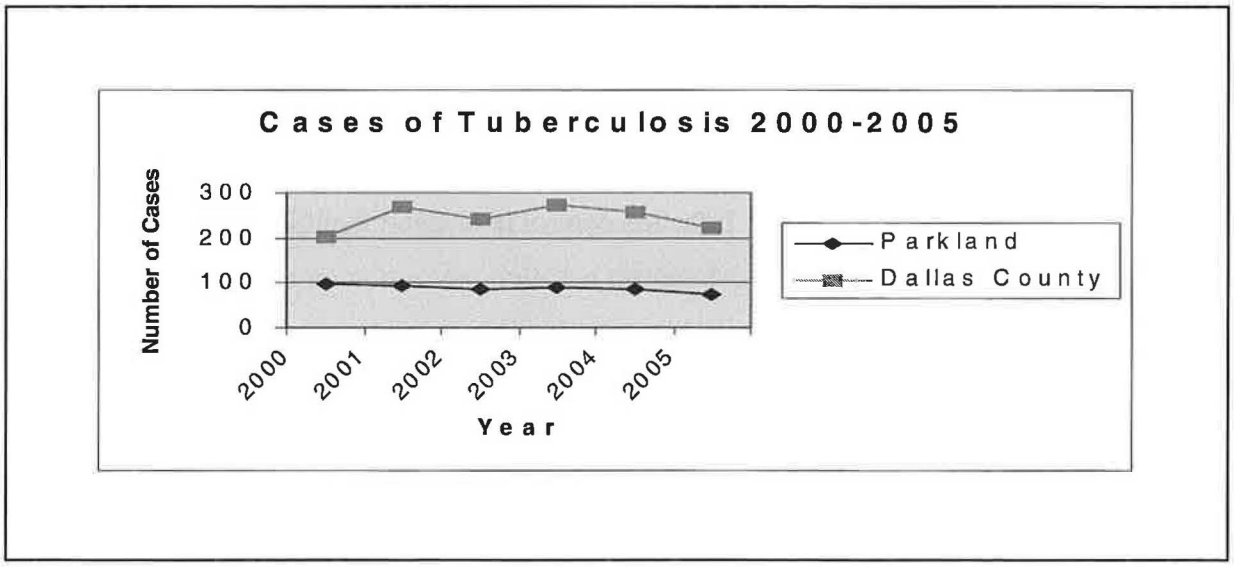
technician was assigned to the MICU to concentrate on implementing these control procedures. After May 2003 there were no new cases in the MICU with this PFGE type. However, beginning in April and continuing through July there occurred 13 cases of *Acinetobacter* in the SICU. These cases were recognized due to cases of clinical disease and active surveillance cultures. PFGE typing of these 13 patient SICU isolates showed that only 3 were identical to the MICU strain so the SICU outbreak probably represented some spillover from the MICU epidemic but for the most part represented new sources of the organism being introduced into the unit. Studies were performed trying to link the MICU to the SICU and this focused on shared equipment such as transport ventilators and Respiratory Therapy personnel traveling between the units.

Acinetobacter is an ICU pathogen which is becoming increasing prevalent. It is a gram negative aerobic rod that is relatively avirulent and found in dirt and water in the environment and in ICU settings. *Acinetobacter* species can be typed by antibiotic susceptibilities and by PFGE. It can cause wound infections and osteomyelitis, pneumonia, ventilator associated pneumonia, urinary tract infections, bacteremia and meningitis. In ICU settings, it is associated with ventilators, nasopharyngeal colonization, and ventilator associated pneumonia. *Acinetobacter* is usually antibiotic resistant and it becomes increasingly resistant the longer it is transmitted in units. Initially, strains are susceptible to tobramycin, amikacin, imipentem and meropenem. Some isolates are susceptible to the new antibiotic, tigecycline. It usually remains susceptible to colistin. A major problem is for *Acinetobacter* to become established in the unit and become more and more antibiotic resistant so that the use of colistin is necessitated. Colistin is a toxic antibiotic, being nephrotoxic and neurotoxic. *Acinetobacter* has become a major pathogen in soldiers wounded in Iraq and Afghanistan. Between January 1, 2002 and August 31, 2004, there were 102 positive blood cultures of *Acinetobacter baumanii* in soldiers from this theater. It was thought that there were introductions of the organism by wound contamination from dirt or a water source and hospital spread of the organism to other patients. The organism caused wound infections, osteomyelitis, urinary tract infections, ventilator associated pneumonia and bacteremia. Infection control in hospital facilities required admission cultures of wounds, axillae, and groin and contact isolation precaution on admission. The contact isolation precautions continued if any culture became positive.

Acinetobacter is part of the of SPACE acronym. This acronym includes the following organisms: *Serratia, Pseudomonas, Acinetobacter, Citrobacter*, and *Enterobacter*. All of the SPACE organisms possess at least one common mechanism of resistance. They possess constitutive chromosomal broad spectrum beta-lactamases. These enzymes are usually repressed and the initial antibiotic resistance pattern may indicate susceptibility in isolates because of this repression. Although initial antibiotic susceptibilities may indicate that a drug like cefotaxime may be effective, use of this drug derepresses the beta- lactamases and isolates then show broad beta-lactam resistance. Eventually, under antibiotic pressure, use of colistin may be necessary. Colistin is dosed as 2.5 -5mg per day usually as a q 12 h dose In Iraq, Afghanistan, and U.S. military hospitals *Acinetobacter* has become a "superbug", that is an extensively antibiotic resistant organism which may potentially outpace our capacity to treat patients.

Tuberculosis

The peak years for tuberculosis admissions to Parkland Memorial Hospital after 1980 were in 1993 with 151 cases and 1994 with 142 cases. Tuberculosis skin test conversion rates in employees after 1980 peaked at 3.7% in 1995 2.4% in 1994 and 2.9% in 1993. These peak years coincided with the period of maximum mortality of the AIDS epidemic which was in 1995 the year before the introduction of protease inhibitors. With improvement in the management of AIDS and better control of the disease process, fewer persons with HIV and latent tuberculosis infection (LTBI) progressed to active TB. Since 1997, tuberculin skin test (TST) conversion rates in Parkland employees are usually less than 1% per year with compliance rates being greater than 90%. Figure 11



shows tuberculosis cases hospitalized at PMH from 2000-2005 and it can be seen that cases are tending to decline with the number of cases in 2006 being 74. Parkland hospitalizes about half of the cases of tuberculosis occurring in Dallas County each year.

Since 1980 there have been 4 epidemics of tuberculosis at Parkland Hospital. The first epidemic involved a case who had just been placed on chemotherapy that had to be intubated in the emergency room and subsequently reintubated. Exposure to the case resulted in 47 TST conversions and 6 cases of active disease. It was suspected but never completely proven that one patient in the emergency room at that time may have contracted tuberculosis from this case and later died of that disease. That patient had active systemic lupus erythematosis and was on immunosuppressive therapy. The second epidemic occurred in the Coronary Care Unit. Employees, including physicians were exposed to an unsuspected case in an employee who had a chronic cough and weight loss. Finally the employee was worked- up and active pulmonary tuberculosis was diagnosed. That case resulted in 43 TST conversions and 2 cases of active disease. The third epidemic occurred in a social service worker who was exposed to a patient case and subsequently developed tuberculosis. She became symptomatic with a cough and exposure to her resulted in 10 TST conversions. The last epidemic occurred in the Physical Medicine and Rehabilitation Department and involved a case of unsuspected wound and pulmonary tuberculosis and resulted in 11 TST conversions.

About 50% of new cases of tuberculosis at Parkland are smear negative but culture positive (S-, C+). Of 86 cases seen in 2004, 20 % were homeless, 21% were HIV antibody positive, and 21% had a jail history. Forty-four percent of patients were African American and 40% had a Hispanic surname. Of the 42 patients listed as foreign born, 25 were from Mexico. Multidrug resistant TB (MDRTB) is seen infrequently at the hospital and is defined by INH and rifampin resistance. A case was found in 2006 of one patient with a Hispanic surname that was in the Dallas County Jail and was admitted to the hospital for care. Extensively drug resistant TB (XDRTB) has not been recognized at the hospital.

Critical to understanding the epidemiology of *M. tuberculosis* in Dallas County is an investigation made by CDC and the Texas Department of Health (TDH) which centered around Cluster 242. The TDH was performing PFGE typing of all TB isolates that were submitted. From 1996 through 2000, 72 patients from the DFW area had a single PFGE TB type. Sixty-six of the 72 patients were from Dallas and 50 of the cases were seen at Parkland Health and

Hospital Services. Seventy-seven percent were African American, 76% male, and 60% were in persons 30-44 years of age. HIV was the most common medical risk and the patients were most commonly at PMH, the HIV clinic, the jail, homeless shelters and the "carwash", which was a center for illicit drug handling and injection. Cluster 242 represented a network of contemporaneous TB transmission. This cluster probably still exists although it is no longer being studied. The investigation found no transmission of TB at the hospital, but recommendations were made about its management, the most significant of which were to involve the Health Department early after admission, making certain that patients had reasonable places to go at discharge and were receiving directly observed therapy (DOT).

Principles of TB isolation are derived its microbiology and epidemiology. Transmission of *M. tuberculosis* occurs almost exclusively from the production of infected aerosols with droplet nuclei. These droplet nuclei consist of single particles of MTB and remain suspended in air and circulate according to air flow. When that air is inhaled, the infective particles are deposited into the alveoli where multiplication occurs and primary tuberculosis develops. A cough that produces respiratory droplets which settle in the dust are not of major significance in transmission. Certain patients are capable of creating highly infectious aerosols. A useful concept is that of the "dangerous disseminator". This concept was investigated and verified by the work of Riley and his collaborators in a series of classical papers published from 1956 -1961. They studied tuberculosis transmission in a Baltimore VA hospital in a ward of 6 rooms each containing a single patient. All of the air from this ward was vented upstairs to a room with multiple cages housing individual guinea pigs. They studied the guinea pigs to determine whether they developed active disease or a positive TST. By studying patient and guinea pig isolates, their biochemical characteristics and their antibiotic susceptibilities, they made important observations about the nature of the infectivity of individual patients. Of 59 patients that were not on chemotherapy, these investigators found that only 7 actually transmitted MTB. One of these seven, a man with laryngeal TB infected 15 guinea pigs over a period of three days. They estimated that he was as infectious as a case of measles (Rubeola). They showed that cases on effective chemotherapy were infrequently infectious for guinea pigs. These investigators theorized that during and after aerosolization, INH became concentrated around droplet nuclei and impaired the infectivity of the organisms. However, Loudon grew organisms in the presence and absence of INH, created aerosols from the broth culture, and inoculated the aerosols into

culture. Over a 12 hour period in an aerosol, he could not demonstrate a difference in culture positivity in samples taken at different times. Riley and his associates also showed that ultraviolet germicidal irradiation (UVGI) was effective in decontaminating the air from rooms of patients with TB. In their studies, patients who had drug resistant organisms were shown to be infectious but not as much as patients with untreated active disease who had susceptible organisms. The observations of Riley and associates were made in 1956-1961 and have not been repeated. There was a wide variability in guinea pig infectivity in untreated patients and no untreated patients were followed before and after effective chemotherapy. The concept of the "dangerous disseminator" and the variability of infectivity in untreated patients are critical to an understanding of the epidemiology of TB. Also critical to the understanding of the transmission of TB is information about epidemics which usually arise from unrecognized cases or cases that have not been treated or are just beginning chemotherapy. Observations in India, in Arkansas, Baltimore, and New York City have shown that patients on effective chemotherapy for a period to time do not infect other contacts. In Madras, India, it was found that most TB patients infected their contacts before they were placed on chemotherapy and usually did not subsequently infect other persons. Although most patients infect their contacts before starting chemotherapy, is probable that treated S+C+ patients can still transmit the disease. The smear positivity of a case is the best estimate of the contagiousness of patients.

Currently, the recognition of MDRTB and knowledge of the epidemics that occurred in the 1990's in association with HIV antibody positive patients complicate the management of cases. It is critical to recognize MDRTB and make sure that isolation occurs until that organism can no longer be transmitted (smear negativity). MDRTB epidemics are critically important in understanding the CDC guidelines for TB isolation. These guidelines state that a patient with TB who is on 4 drug chemotherapy and who is having a clinical and bacteriological response can be discharged from the hospital when 3 sputum samples observed over 24 hour are smear negative. If the patient is smear positive (S+), they can be sent home on chemotherapy, if contacts have been previously exposed and if there are no infants or children < 4 or immunosuppressed persons in the home. These guidelines direct that there should be coordination between the Health Department for follow-up and DOT.

There were 74 patients with active TB hospitalized at Parkland Memorial Hospital during 2006. Twenty three of these patients had cavitary TB on admission, 19 of whom were S+C+ and

4 of whom were S-C+. On discharge, 9 patients were S+, 6 were S-, 6 were indeterminate which usually meant that sputum smears and cultures were not done. Sixteen of the patients were discharged home, 2 died during the hospitalization, 2 were sent to Tyler, Texas to the East Texas State Hospital, 1 was sent to San Antonio to the Tuberculosis Sanitorium outside of the city, 2 patients had an unknown discharge status or were sent to a shelter. One of these later 2 patients was S-C+ and the other patient's smear status is unknown because it was not done. Of the 2 patients who were unknown or sent to a shelter, both later returned and had to be hospitalized with active TB. Both were rehospitalized at Parkland with one being transferred to San Antonio. The number of days on RIPE before discharge ranged between 1 and 39 days with a median value of 5 and a mean of 8.8 days, a mode of 4. Four cases had less than 4 days of effective chemotherapy.

In managing patients with TB at PMH, suspect TB particularly in high risk groups. Isolate suspected cases promptly; patients can always be moved from isolation. Fifty percent of new cases are S-, C+. Start suspected cases on 4 drug chemotherapy. Plan management for discharge early and this includes home placement and whether they have to be sent to other hospitals in Tyler or San Antonio. Get patients scheduled for DOT and make contact with the Dallas County Health Department. Usually, patients should show a clinical and bacteriological response before discharge.

REFERENCES

Methicillin-Resistant Staphyococcus aureus (MRSA)

1. Boyce J., White R., Causey W., Lockwood W. 1983. Burn Units As A Source Of Methicillin-Resistant Staphyococcus aureus Infections. JAMA, 249:2803-2807.

2. Chambers H. 2005. Community-Associated MRSA-Resistance And Virulence Converge. NEJM, 352:1485-1487.

3. Cooper B., Stone S., Kibbler C., Cookson B., Roberts J., Medley G., Duckworth G., Lai R., Ebrahim S. 2004. Isolation Measures In The Hospital Management Of Methicillin Resistant Staphylococcus aureua (MRSA): Systematic Review Of The Literature. BMJ, 329:533-541.

4. Haley R., Cushion N., Tenover F., Bannerman T., Dryer D., Ross J., Sanchez P., Siegel J. 1995. Eradication Of Endemic Methicillin-Resistant Staphylococcus aureus Infections From A Neonatal Intensive Care Unit. Journal Of Infectious Disease 171:614-624.

5. Hota B. 2006. Infection Control Or Formulary Control: What Is The Best Tool To Reduce Nosocomial Infections Due To Methicillin-Resistant Staphylococcus aureus? Clinical Infectious Diseases, 42:785-787.

6. Huang H., Flynn N., King J., Monchaud C., Morita M., Cohen S. 2006. Comparisons Of Community-Associated Methicillin-Resistant Staphylococcus aureus (MRSA) And Hospital-Associated MSRA Infections In Sacramento, CA. Journal Of Clinical Microbiology, 44:2423-2427.

7. Hunt J., Purdue G., Tuggle D. 1988. Morbidity And Mortality Of An Endemic Pathogen: Methicillin-Resistant Staphylococcus Aureus. The American Journal Of Surgery, 156:524-528.

8. Kollef M. 1999. The Prevention of Ventilator-Associated Pneumonia. NEJM, 340:627-634.

9. Meier P., Carter C., Wallace S., Hollis R., Pfaller M., Herwaldt L. 1996. A Prolonged Outbreak Of Methicillin-Resistant Staphylococcus aureus In The Burn Unit Of A Tertiary Medical Center. Infection Control Hosp. Epidemiology, 17:798-802.

10. Miller L., Quan C., Shay A., Mostafaie K., Bharadwa K., Tan N., Matayoshi K., Cronin J., Tan J., Tagudar G., Bayer A. 2007. A Prospective Investigation Of Outcomes After Hospital Discharge Or Endemic, Community-Acquired Methicillin-Resistant And Susceptible Staphylococcus aureus Skin Infection. Clinical Infectious Diseases, 44:483-492.

11. Nambiar S., Herwaldt L., Singh N. 2003. Outbreak Of Invasive Disease Caused By Methicillin-Resistant Staphylococcus aureus In Neonates And Prevalence In The Neonatal Intensive Care Unit. Pediatric Crit. Care Med., 4:220-226.

12. Shiomori T., Miyamoto H., Makishima K. 2001. Significance Of Airborne Transmission Of Methicillin-Resistant Staphylococcus aureus In An Otolaryngology-Head and Neck Surgery Unit. Arch. Otolaryngol Head and Neck Surg., 127:644-648.

13. Shorr A., Lodise T. 2006. Burden Of Methicillin-Resistant Staphylococcus aureus On Healthcare Cost And Resource Utilization. ISMR Update, 1:1-10.

14. Volturo G., Napolitano L., Shorr A., Stevens D. 2006. The Evolving Challenges Of MRSA Infection -From The Hospital To The Community: Optimizing Prevention, Detection, And Antimicrobial Therapy Of MRSA Pulmonary, Skin, And Soft Tissue Infections. Clinical Consensus Update In Hospital Medicine, 1-41.

15. Weigelt J., Kaafarani M., Itani K., Swanson R. 2004. Linezolid Eradicates MRSA Better Than Vancomycin From Surgical–Site Infections. The American Journal of Surgery, 188:760-766.

16. Wibbenmeyer L., Danks R., Faucher L., Amelon M., Latenser B., Kealey P., Herwaldt L. 2006. Prospective Analysis of Nosocomial Infection Rates, Antibiotic Use, And Patterns Of Resistance In A Burn Population. Journal Burn Care Res., 27:152-160.

17. Wilson R., Huang S., McLean A. 2004. The Correlation Between Airborne Methicillin-Resistant Staphylococcus aureus With The Presence Of MRSA Colonized Patients In A General Intensive Care Unit. Anesthesia And Intensive Care, 32:202-209.

18. Wisplinghoff H., Bischoff T., Tallent S., Seifert H., Wenzel R., Edmond M. 2004. Nosocomial Bloodstream Infections In US Hospitals: Analysis Of 24,179 Cases From A Prospective Nationwide Surveillance Study. Clinical Infectious Diseases, 39:309-317.

Vancomycin Resistant Enterococci (VRE)

1. Farr B. 1998. Hospital Wards Spreading Vancomycin-Resistant Enterococci To Intensive Care Unit: Returning Coals To Newcastle. Crit. Care Med., 26:1942-1943.

2. Gerding D. 1997. Is There a Relationship Between Vancomycin-Resistant Enterococcal Infection And *Clostridium difficile* Infection? Clinical Infectious Diseases, 25: S206-210.

3. Ostrowsky B., Trick W.E., Sohm A., Quirk S., Holt S., Carson L., Hill B., Arduino M., Kuehnert M., Jarvis W. 2001. Control Of Vancomycin-Resistant Enterococcus In Health Care Facilities In A Region, NEJM, 344:1427-1433.

4. Paule S., Trick W.E, Tenover F., Lankford M., Cummingham S., Stosor V., Cordell R., Peterson L. 2003. Comparison Of PCR Assay To Culture For Surveillance Detection Of Vancomycin-Resistant Enterococci. Journal Of Clinical Microbiology, 41:4805-4807.

5. Safdar N. Maki D. 2002. The Commonality Of Risk Factors For Nosocomial Colonization And Infection With Antimicrobial-Resistant Staphylococcus aureus, Enterococcus, Gram-Negative Bacilli, *Clostridium difficile*, And Candida. Annals Internal Medicine, 136:834-844.

6. Siegel J., Rhinehart E., Jackson M., Chiarello L. 2006. CDC Management Of Multidrug-Resistant Organisms In Healthcare Settings. 1-74.

***Clostridium difficile* –associated diarrhea (CDAD)**

1. Bartlett J., Perl T. 2005. The New *Clostridium difficile*-What Does It Mean? NEJM 353:2503-2505.

2. Bartlett J. 2006. Narrative Review: The New Epidemic Of *Clostridium difficile*-Associated Enteric Disease. Annals Of Internal Medicine, 145:758-764.

3. Dallal R., Harbrecht B., Boujoukas A., Sirio C., Farkas L., Lee K., Simmons R. 2002. Fulminant *Clostridium difficile*: An Underappreciated And Increasing Cause Of Death And Complications. Annals Of Surgery, 235:363-372.

4. Dial S., Delaney J., Barkun A., Suissa S. 2005. Use Of Gastric Acid-Suppressive Agents And The Risk Of Community-Acquired *Clostridium difficile*-Associated Disease. JAMA, 294:2989-2995.

5. Gerding D., Johnson S., Peterson L., Mulligan M., Silva J. 1995. *Clostridium difficile*-Associated Diarrhea And Colitis. Infection Control And Hospital Epidemiology, 16:459-477.

6. Kelly C., Pothoulakis C., LaMont T. 1994. *Clostridium difficile* Colitis. NEJM, 330:257-262.

7. Kim K-H., Fekety R., Batts D., Brown D., Cudmore M., Silva J., Waters D. 1981. Isolation Of *Clostridium difficile* From The Environment And Contacts Of Patients With Antibiotic-Associated Colitis. Journal Of Infectious Diseases, 143:42-50.

8. Kyne L., Warny M., Qamar A., Kelly C. 2000. Asymptomatic Carriage Of *Clostridium difficile* And Serum Levels Of IgG Antibody Against Toxin A. NEJM, 342:390-397.

9. Loeb M., Craven S., McGeer A., Simor A., Bradley S., Low D., Armstrong-Evans M., Moss L., Walter S. 2003. Risk Factors For Resistance To Antimicrobial Agents Among Nursing Home Residents. American Journal Of Epidemiology, 157:40-47.

10. Loo V., Poirier L., Miller M., Oughton M., Libman M., Michaud S., Bourgault A., Nguyen T., Frenette C., Kelly M., Vibien A., Brassard P., Fenn S., Dewar K., Hudson T., Horn R., Rene P., Monczak Y., Dascal A. 2005. A Predominantly Clonal Multi-Institutional Outbreak Of *Clostridium difficile*-Associated Diarrhea With High Morbidity And Mortality. NEJM, 353:2442-2449.

11. McDonald C., Killgore G., Thompson A., Owens R., Kazakova S., Sambol S., Johnson S., Gerding D. 2005. An Epidemic, Toxin Gene-Variant Strain Of *Clostridium difficile*. NEJM, 353:2433-2441.

12. McFarland L., Elmer G., Surawicz C. 2002. Breaking The Cycle: Treatment Strategies For 163 Cases Of Recurrent *Clostridium difficile* Disease. The American Journal Of Gastroenterology, 97:1769-1775.

13. McFarland L., Mulligan M., Kwok R., Stamm W. 1989. Nosocomial Acquisition Of *Clostridium difficile* Infection. NEJM, 320:204-210.

14. Muto C., Pokrywka M., Shutt K., Mendelsohn A., Nouri K., Posey K., Roberts T., Croyle K., Krystofiak S., Patel-Brown S., Pasculle A., Paterson D., Saul M., Harrison L. 2005. A Large Outbreak Of *Clostridium difficile*-Associated Disease With An Unexpected Proportion Of Deaths And Colectomies At A Teaching Hospital Following Increased Fluoroquinolone Use. Infection Control And Hospital Epidemiology, 26:273-280.

15. Pepin J., Saheb N., Coulombe M., Alary M., Corriveau M., Authier S., Leblanc M., Rivard G., Bettez M., Primeau V., Nguyen M., Jacob C., Lanthier L. 2005. Emergence Of Fluoroquinolone As The Predominant Risk Factor For *Clostridium difficile*-Associated Diarrhea: A Cohort Study During And Epidemic In Quebec, CID, 41:1254-1260.

16. Pepin J., Valiquette L., Cossette B. 2005. Mortality Attributable To Nosocomial *Clostridium difficile*-Associated Disease During An Epidemic Caused By A Hypervirulent Strain In Quebec. CMAJ, 173:1037-1042.

17. Ticehurst J., Aird D., Dam L., Borek A., Hargrove J., Carroll K. 2006. Effective Detection Of Toxigenic *Clostridium difficile B*y A Two-Step Algorithm Including Tests For Antigen And Cytotoxin. Journal Of Clinical Microbiology, 44:145-1149.

18. Walker R., Ruane P., Rosenblatt J., Lyerly D., Gleaves C., Smith T., Pierce P., Wilkins T. 1986. Comparison Of Culture, Cytotoxicity Assays, and Enzyme-Linked Immunosorbent Assay For Toxin A And Toxin B In The Diagnosis Of *Clostridium difficile*-Related Enteric Disease. Diagnosis Microbiology Infectious Disease, 5:61-69.

19. Wanahita A., Goldsmith E., Marino B., Musher D. 2003. *Clostridium difficile* Infection In Patients With Unexplained Leukocytosis. American Journal Of Medicine, 115:543-546.

20. Warny M., Pepin J., Fang A., Killgore G., Thompson A., Brazier J., Frost E., McDonald C. 2005. Toxin Production By An Emerging Strain Of *Clostridium difficile* Associated With Outbreaks Of Severe Disease In North America And Europe. The Lancet, 366:1079-1084.

Acinetobacter an ICU Pathogens

1. Aarabi B. 2004. Comparative Study Of Bacteriological Contamination Between Primary And Secondary Exploration Of Missile Head Wounds. Neurosurgery, 20:610-616.

2. Acinetobacter baumanii Infections Among Patients At Military Medical Facilities Treating Injured U.S. Service Members, 2002-2004. MMWR, 53(45):1063-1066.

3. Ayan M., Durmaz R., Aktas E., Durmaz B. 2003. Bacteriological, Clinical And Epidemiological Characteristics Of Hospital-Acquired *Acinetobacter baumanii* Infection In A Teach Hospital. Journal Of Hospital Infection, 54:39-45.

4. Aygun G., Demirkiran O., Utku T., Mete B., Urkmez S., Yilmaz M., Yasar H., Dikmen Y., Ozturk R. 2002. Environmental Contamination During A Carbapenem-Resistant *Acinetobacter baumanii* Outbreak In An Intensive Care Unit. Journal Of Hospital Infection, 52:259-262.

5. Catalano M., Quelle L. Jeric P., Martino A., Maimone S. 1999. Survival Of *Acinetobacter baumanii* On Bed Rails During An Outbreak And During Sporadic Cases. Journal Of Hospital Infection, 42:27-35.

6. Davis K., Moran K., McAllister K., Gray P. 2005. Multidrug-Resistant *Acinetobacter* Extremity Infections In Soldiers. Emerging Infectious Diseases, 11:1218-1224.

7. Landman D., Quale M., Mayorga D., Adedeji A., Vangala K., Ravishankar J., Flores C., Brooks S. 2002. Citywide Clonal Outbreak Of Multiresistant *Acinetobacter baumanii* And *Pseudomonas aeruginosa* In Brooklyn, NY; The Preantibiotic Era Has Returned. Arch Internal Medicine, 162:1515-1520.

8. Levin A., Barone A., Penco J., Santos M., Marinho I., Arruda E., Manrique E., Costa S. 1999. Intravenous Colistin As Therapy For Nosocomial Infections Caused By Multidrug-Resistant *Pseudomonas aeruginosa* And *Acinetobacter baumanii.* Clinical Infectious Diseases, 28:1008-1011.

9. Looveren M., Goossens H., ARPAC Steering Group. 2004. Antimicrobial Resistance Of *Acinetobacter* spp. in Europe. Clinical Microbiology And Infectious Diseases, 10:684-704.

10. Poutanen S., Louie M., Simor A. 1997. Risk Factors, Clinical Features And Outcome Of *Acinetobacter* Bacteremia In Adults. Eur. J. Clinical Microbiology Infectious Diseases, 16:737-740.

11. Tong M. 1972. Septic Complications Of War Wounds. JAMA, 219:1044-1047.

12. Tuma R. Multidrug-Resistant Acinetobacter Hitchhiking To US Military Hospitals Wounded Soldiers: Presented At IDSA.

13. Urban C., Segal-Maurer S., Rahal J. 2003. Considerations In Control And Treatment Of Nosocomial Infections Due To Multidrug-Resistant *Acinetobacter baumanii.* Clinical Infectious Diseases, 36:1268-1274.

14. Villegas M., Hartstein A. 2003. *Acinetobacter* Outbreaks, 1977-2000. Infection Control And Hospital Epidemiology, 24:284-295.

15. Volpin G., Krivoy N., Stein H. 1993. Acinetobacter sp. Osteomyelitis Of The femur: A Late Sequel Of Unrecognized Foreign Body Implantation. Injury. International Journal Of The Care Of The Injured, 24:345-346.

16. Weinbren M.J., Borthwick M.A. 2004. Rapid Detection Of Extended-Spectrum B-lactamase (ESBL)-Producing Organisms In Blood Cultures. Journal Of Antimicrobial Chemotherapy, 55:131-132.

17. Wendt C., Dietze B., Dietz E., Ruden H. 1997. Survival Of *Acinetobacter baumanii* On Dry Surfaces. Journal Of Clinical Microbiology, 35:1394-1397.

18. Wisplinghoff H., Perbix W., Seifert H. 1999. Risk Factors For Nosocomial Bloodstream Infections Due To *Acinetobacter baumanii*: A Case-Control Study Of Adult Burn Patients. Clinical Infectious Disease, 28:59-66.

19. Wisplinghoff H., Edmond M., Pfaller M., Jones R., Wenzel R., Seifert H. 2000. Nosocomial Bloodstream Infectious Caused By *Acinetobacter* Species In United States Hospitals: Clinical Features, Molecular Epidemiology, And Antimicrobial Susceptibility. Clinical Infectious Diseases, 31:690-697.

Tuberculosis

1. Abeles H. 1973. Early Hospital Discharge of Tuberculosis Patients With Sputum Containing Acid-Fast Bacilli On Microscopic Examination. American Review Of Respiratory Disease, 108.

2. Adler J. 1993. Hospital-Acquired Tuberculosis: Addressing the Challenge. Hospital Practice, 109-120.

3. American Thoracic Society/Center For Disease Control And Prevention/Infectious Diseases Society Of America: Treatment Of Tuberculosis. 2003. American Journal Of Respiratory Crit. Care Med., 167:603-662.

4. Brooks S., Lassiter N., Young E. 1973. A Pilot Study Concerning The Infection Risk Of Sputum Positive Tuberculous Patients On Chemotherapy. American Review Of Respiratory Disease, 108:799-804.

5. Catanzaro A. 1982. Nosocomial Tuberculosis. Am. Rev. Respir. Dis., 125:559-562.

6. Colditz G., Brewer T., Berkey C., Wilson M., Burdick E., Fineberg H., Mosteller F. 1994. Efficacy Of BCG Vaccine In The Prevention Of Tuberculosis. JAMA, 271:698-702.

7. Department Of Health And Human Services, CDC Prevention, Draft Guideline For Isolation Precautions In Hospital; Notice. 1994. Federal Register, 59(214):55552-55569.

8. Department Of Health And Human Services CDC Guidelines For Preventing The Transmission Of *Mycobacterium Tuberculosis* In Health Care Facilities. 1994. Federal Register, 59(208):54241-54303.

9. Earnest M., Sbarbaro J. 1995. Defining The Issues: Returning Patients With Tuberculosis To Institutional Settings. Clinical Infectious Diseases, 20:497-500.

10. Fine P. 1995. Bacille Calmette-Guerin Vaccines: A Rough Guide. Clinical Infectious Diseases, 20:11-4.

11. George R., Gully P., Gill O., Innes J., Bakhshi S., Connolly M. 1985. An Outbreak Of Tuberculosis In A Children's Hospital. The Hospital Infection Society, 30:129-142.

12. Haley C., McDonald R., Rossi L., Jones W. Jr., Haley R., Luby J. 1989. Tuberculosis Epidemic Among Hospital Personnel. Infect. Control Hospital Epidemiology. 10(5):204-210.

13. Hospitalization & Community Discharge Of TB Patients Protocol. 2004. New York City, Dept. Of Human And Mental Health, 104:1-19.

14. Jensen P., Lambert L., Iademarco M., Ridzon M. 2005. CDC Guidelines For Preventing The Transmission Of *Mycobacterium tuberculosis* In Health-Care Setting, 1-182.

15. Kantor H., Poblete R., Pusateri S., 1988. Nosocomial Transmission Of Tuberculosis From Unsuspected Disease. The American Journal Of Medicine, 84: 833-838.

16. Kim T., Blackman R., Heatwole K., Kim T., Rochester D. 1984. Acid-Fast Bacilli In Sputum Smears Of Patients With Pulmonary Tuberculosis. Prevalence And Significance Of Negative Smears Pretreatment And Positive Smears Post-Treatment. Am. Rev. Respir. Dis., 129:264-268.

17. Loudon R., Bumgarner L., Coffman G. 1969; Isoniazid and the Survival of Tubercle Bacilli in Airborne Droplet Nuclei. American Review of Resp. Disease 100: 172-17

18. Mathew P., Kuo Y., Vazirani B., Eng R., Weinstein M. 2002. Are Three Sputum Acid-Fast Bacillus Smears Necessary For Discontinuing Tuberculosis Isolation? Journal Of Clinical Microbiology, 40:3482-3484.

19. McGowan J. 1995. Nosocomial Tuberculosis: New Progress In Control And Prevention. Clinical Infectious Diseases, 21:489-505.

20. Menzies D. 1997. Effect Of Treatment On Contagiousness Of Patients With Active Pulmonary Tuberculosis. Infection Control Hospital Epidemiology, 18:582-586.

21. Mitchison D. 1990. Infectivity Of patients With Pulmonary Tuberculosis During chemotherCpy. Eur. Respir. Journal, 3:385-386.

22. Mixides G., Shende V., Teeter L., Awe R., Musser J. Graviss E. 2005. Number Of Negative Acid-Fast Smears Needed To Adequately Assess Infectivity Of Patients With Pulmonary Tuberculosis. Chest, 128:108-115.

23. Nelson T. 1994. Devices For The Prevention Of TB Transmission, Considerations For Proper Application. Journal Of Healthcare Material Management, 22-27.

24. Noble R. 1981. Infectiousness Of Pulmonary Tuberculosis After Starting Chemotherapy: Review Of The Available Data On An Unresolved Question. Associated Practice Infection Control, 9:6-10.

25. Pearson M., Jereb J., Frieden T., Crawford J., Davis B., Dooley S., Jarvis W. 1992. Nosocomial Transmission Of Multidrug-Resistant *Mycobacterium tuberculosis*; A Risk To Patients And Health Care Workers. Annals Of Internal Medicine, 117:191-196.

26. Raviglione M., Smith I. 2007. XDR Tuberculosis-Implications For Global Public Health. NEJM, 356:656-659.

27. Riley, R., Wells W., Mills C., Nyka W., McLean R. 1957. Air Hygiene In Tuberculosis: Quantitative Studies Of Infectivity And Control In A Pilot Ward, American Review In Tuberculosis, 75:420-431.

28. Riley, R, 1957. Aerial Dissemination Of Pulmonary Tuberculosis (Amberson Lecture), American Review of Tuberculosis, 76:931.

29. Riley R., Mills C., Nyka W., Weinstock N., Storey P.B., Sultan L.U., Riley, M.C., Wells W.F. 1959. Aerial Dissemination Of Pulmonary Tuberculosis: A Two-Year Study Of Contagion In A Tuberculosis Ward, Amer. J Hyg., 70:185-196.

30. Riley R., Mills F., O'Grady F., Sultan L., Wittstadt F., Shivpuri D. 1962. Infectiousness Of Air From A Tuberculosis Ward. Amer. Rev. Respir. Dis., 85:511525.

31. Sepkowitz K. 1994. Tuberculosis And The Health Care Worker: A Historical Perspective. American College of Physicians, 120:71-79.

32. Sepkowitz K. 1996. How Contagious Is Tuberculosis? Clinical Infectious Diseases, 23:954-962.

33. Shaw J., Wynn-Williams N. 1954. Infectivity Of Pulmonary Tuberculosis In Relation To Sputum Status. Am Rev. Tuber., 69:724-732.

34. Sultan, L., Nyka W., Mills C., O'Grady F, Wells W., Riley R. 1960. Tuberculosis Disseminators: A Study Of The Variability Of Aerial Infectivity Of Tuberculous Patients, American Review Respiratory Disease, 82:358-369.

35. Telzak E., Fazal B., Pollard C., Turett G., Justman J., Blum S. 1997. Factors Influencing Time To Sputum Conversion Among Patients With Smear-Positive Pulmonary Tuberculosis. Clinical Infectious Diseases, 25:666-670.

36. Yeager H. Jr., Lacy J., Smith L., LeMaistre C. 1967. Quantitative Studies Of Mycobacterial Populations In Sputum And Saliva. American Review Respir. Dis., 95:998-1004.