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RECURRANCE OF MULTIDRUG-RESISTANT ENTEROCOCCI IN A NEUTROPENIC PATIENT

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Over the past 20 years, multidrug-resistant enterococci (MDRE) have emerged as a leading cause of nosocomial infections. Its importance stems not only from its increasing incidence among high-risk hospital populations, but also from the lack of established effective therapy in eradicating the pathogen. There is increasing awareness of MDRE reservoirs in settings such as oncology wards, intensive care units, and hemodialysis units. A predilection for patients with severe underlying illness has been commonly observed. We present a patient with persistent MDRE colonization over a four-month period of time, along with recurrent MDRE bloodstream infections during periods of neutropenia in separate hospitalizations.

A 37-year-old man was diagnosed with non-Hodgkin’s lymphoma with central nervous system involvement in March 1995. He was allergic to penicillin and sulfa drugs. He received systemic and intrathcal chemotherapy. Fever developed during the ensuing neutropenia, and an enterococcus species that was resistant to all antibiotics tested, including vancomycin, penicillin, ampicillin, and gentamicin, grew in blood cultures. A combination of antibiotics including vancomycin, ciprofloxacin, and aminoglycosides were administered for two weeks. Subsequent blood cultures during that hospitalization were negative, as were stool and cerebrospinal fluid cultures. A urine culture positive for MDRE was obtained shortly after discharge and was treated on an outpatient basis with oral ciprofloxacin 500 mg every 12 hours. Repeat cultures were not performed. On the patient’s subsequent hospitalization in May 1995, MDRE was isolated from a urine culture with negative blood cultures. In the month of July, he was hospitalized for the third course of chemotherapy. He developed fevers, mucositis, and severe pain of the right abdomen and thigh with normal-appearing skin that subsequently progressed to erythema with a large, necrotic center and bullae formation (Fig 1). Blood cultures at this time were positive for the MDRE species, as was a culture of the involved skin. Stool and CSF cultures were negative for Enterococcus. After desensitization to penicillin, a combination of vancomycin, ampicillin/subactam, gentamicin, and ofloxacin was begun. The central venous catheter was removed. A subsequent blood culture four days later was negative. In the next few weeks, the patient improved with resolution of his fevers and containment of the cellulitis (Fig 2). He was not considered a surgical candidate. His clinical condition quickly deteriorated during the following week, and he died in early August of a combination of sepsis with multi-organ system failure and persistent neutropenia with persistently negative blood cultures.

Enterococci form part of the normal flora of the gastrointestinal tract and female genitourinary tract. The emergence of enterococci as a major nosocomial pathogen has received considerable attention during the past decade due to reports of Enterococcal/vancomycin-resistant enterococci spread by direct patient-to-patient contact and by indirect transmission via hospital personnel, environmental surfaces, and hospital equipment. This, coupled with the progressive increase in resistance — first to aminoglycosides, followed by ampicillin and vancomycin — poses a serious challenge to the treatment and eradication of this infection. While VRE in Europe may be thought to form part of normal fecal flora, VRE/MDRE in the United States appears to target those with severe underlying infections, or immunosuppression, a preponderant population at oncology centers such as ours. In 1993, the Centers for Disease Control and Prevention (CDC) reported a 20-fold increase in the proportion of nosocomial VRE throughout the United States between 1989 and 1993. In 1988, the first outbreak of VRE was reported by Uttley et al, followed by numerous outbreaks reported since then. The National Nosocomial Infections Surveillance System has reported that between 1989 and 1993, nearly 4% of nosocomial enterococcal bacteremia were resistant to vancomycin, and total VRE isolates increased from 0.3% to 7.9%. Similar increases have been reported in intensive care units and non-intensive care units by the CDC.
during the same time period. These figures have been gathered from small numbers of patients, mainly during localized outbreaks, but it is evident that VRE is becoming endemic in numerous hospitals across the nation. Uniform consensus as to the appropriate intervention remains to be elucidated.

Extensive or multiple hospitalizations show a correlation with the subsequent development of VRE/MDRE infections, as does mucositis, prior antibiotic treatment, prolonged stay within intensive care units, and, in some instances, even intrahospital transfers. It has been suggested that intensive care units may become reservoirs for VRE, thus enabling dissemination within the hospital. The overall mortality of these patients has been estimated to be between 35% and 40%. While outbreaks of VRE have been associated with a higher mortality rate, it should be noted that severity of illness has been described as an independent risk factor for VRE acquisition. Not surprisingly, the precise cause of death in nearly half of the deceased patients can be ascribed to their underlying illness.

VRE isolates are most commonly found in stool, urine, wound, and blood cultures. Persistent colonization of the gastrointestinal and urinary tract has been reported to result in repeated bloodstream infections in neutropenic patients despite extended periods outside the hospital. Our patient’s recurrent infections coincided with the onset of neutropenia and mucositis, along with extended antibiotic therapy. Unfortunately, we did not perform nucleic acid homology studies in order to ascertain whether the isolates were identical.

The daunting problem of treating VRE is well described, and the absence of effective prophylaxis makes it imperative to focus our attempts on early detection and prevention of nosocomial spread of this pathogen among patients at risk of developing serious infection. In accordance with recommendations by the Hospital Infection Control Practices Advisory Committee, contact isolation for those patients with known history of VRE infection or colonization is prudent. Surveillance rectal swab cultures upon repeat admission for these patients are routinely done at our center. In our experience as well as that found in literature, the prognosis of a VRE-infected cancer patient is associated with the severity and duration of neutropenia and remission of cancer.

Effective therapy for MDRE has not been determined. Streptogramins used alone or in combination have activity against MDRE, but failures still occur. We obtained a 100% bacteriologic cure with combination antimicrobial therapy using vancomycin, gentamicin, ampicillin/sulbactam, and imipenem/cilastatin. However, several patients die in septic shock with persistent neutropenia despite sterilization of the bloodstream. Eradication of MDRE colonization is needed to prevent further spread when neutropenia occurs. Curtailing the liberal use of vancomycin empirically in febrile neutropenic patients is another strategy to reduce VRE infection rates. Finally, immediate contact isolation upon admission of patients known to be colonized presently or in the past may be a prudent measure to limit intrahospital spread.

Another strategy to prevent recurrent VRE infections during subsequent periods of neutropenia is gut decontamination with oral agents such as bacitracin, which is frequently used for bowel decontamination in colorectal surgeries. A combination of antimicrobials will probably be necessary to adequately treat MDRE bacteremia in neutropenic patients. One combination that may provide adequate coverage is a streptogramin (quinupristin/dalfopristin — not approved by the Food and Drug Administration) and minocycline. In line with human immunodeficiency virus and many malignancies, MDRE will most likely require combination antimicrobial modalities with differing mechanisms of action.

References


