EDITORIAL

ACINETOBACTER : A PERSPECTIVE

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ABSTRACT

***Acinetobacter calcoaceticus* is a common bacterial isolate from hospital clinical specimens. Careful consideration must be taken to distinguish colonization from true infection. Clinical syndromes associated with Acinetobacter include cellulitis, bacteremia, respiratory tract, urinary tract and central nervous system involvement. The patient may be asymptomatic or fulminantly ill. Therapy is determined by the site of the infection and the patient's symptomatology. Acinetobacter expresses multiple antibiotic resistance via chromosomal-and plasmid-mediated resistance genes. Some antibiotic resistance enzymes may be inactivated by β-lactamase inhibitors. One such compound, sulbactam, has allowed antibiotics once ineffective against Acinetobacter to become useful again. In serious infections with Acinetobacter a combination of drugs is indicated to prevent resistance from developing. Careful attention to handwashing and determining the common source in Acinetobacter epidemics is the only way to control the spread of this pathogen.**

Keywords: Plasmid-mediated resistance, β-lactamase inhibitors, sulbactam

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I. INTRODUCTION

Acinetobacter calcoaceticus was the fourth most common bacterial isolate from clinical specimens submitted to the Bacteriology laboratory of Singapore General Hospital in 1988[1]. Finding this ubiquitous, relatively avirulent, Gram negative organism often provokes a clinician's indecision regarding its role in the patient's condition and the need for therapy. We hope to clarify the significance of Acinetobacter isolation and provide a practical approach to management in the following review. We will discuss the epidemiology, prevalence, diagnosis, therapeutic options and means of preventing Acinetobacter infections. A case demonstrating a unique strategy to counter Acinetobacter antimicrobial resistance is also provided.

II. HISTORY AND EPIDEMIOLOGY

Acinetobacter calcoaceticus is a coccobacillary Gram negative organism ubiquitous in nature and commensal in humans. As a result of multiple independent discoveries and the lack of standard microbiologic nomenclature in the early 20th century, Acinetobacter acquired a long list of now obsolete names: *Herellea vaginicola, Bacterium anitratum,* and *Mima polymorphea* among others. In current taxonomy, Acinetobacter has been assigned to the Family Neisseriaceae with genera *Neisseria, Kingella,* and *Moraxella.* The single species, *Acinetobacter calcoaceticus,* is comprised of two variants: *Acinetobacter calcoaceticus* var. *anitratus* and var. *Iwoffi.* The majority of clinical isolates outside of the urinary tract are the more antibiotic-resistant *A. calcoaceticus* var. *anitratus.*

Unlike other members of this Family, Acinetobacter's metabolic opportunism allows it to thrive on inanimate as well as animate objects[2,3]. All properly cultured environmental soil and water samples will yield Acinetobacter[4]. In the hospital setting, Acinetobacter has been cultured from soap dishes, washcloths, bedside urinals, ventilators, angiography catheters, peritoneal dialysis fluid, and the hands of hospital personnel[5] Omnipresence in the hospital and transmission via the hands of personnel result in frequent patient colonization[6]. As a consequence, microbiological specimens indiscriminately collected will often be contaminated with Acinetobacter. Records from the Microbiology Department of Singapore General Hospital found Acinetobacter to follow *Staphylococcus aureus, Klebsiella* sp., and *Eschericia coli* in frequency of isolation from submitted specimens in 1988[1].

III. PATHOGENESIS AND THERAPY

Acinetobacter is a relatively avirulent organism lacking specific toxins, adherence factors, or the ability to survive intracellularly. Colonization of skin, mucous membranes and foreign bodies is much more common than true infection. Tissue invasion is limited without a predisposing defect in the host's defense. Hospitalized patients with intravenous lines, indwelling urinary catheters, wounds, devitalized tissue, tracheostomies, endotracheal

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intubation, and poor nutritional status are ideal hosts for Acinetobacter infection.

The need for antimicrobial therapy is determined by the clinical relevance of the isolate. Colonization requires no therapy or further investigation. For cellulitis, tracheobronchitis and lower urinary tract infections, local measures including debridement, pulmonary hygiene and catheter removal, respectively, are often sufficient. Patients with pneumonia, pyelonephritis, meningitis or symptomatic bacteremia will require systemic antibiotics.

The speed at which Acinetobacter isolates have acquired multiple antibiotic resistance has affected treatment recommendations[7,8]. The last ten years has seen previously useful drugs become ineffective: ampicillin, carbenicillin, cefoxitin, cefotaxime, gentamicin, chloramphenicol, etc. As a consequence, combination therapy has been recommended to assure adequate organism eradication in life-threatening infections and in infections that will require long-term therapy. Combination therapy is more for the theoretical prevention of resistance development than the need for synergistic bacterial killing. Therefore, patients with mild to moderate infections with *Acinetobacter calcoaceticus* (eg. pyelonephritis, tracheobronchitis unresponsive to local measures, etc.) can be treated with an effective single agent. Those with life-threatening infections (eg. septic shock, symptomatic bacteremia or pneumonia) and those requiring those long-term therapy (eg. endocarditis and osteomyelitis) should be treated with an active β-lactam plus an aminoglycoside.

IV. PRACTICAL GUIDE TO MANAGEMENT

Acinetobacter has been implicated as an opportunistic pathogen in a wide variety of clinical syndromes. The most frequent presentations include: cellulitis, respiratory tract infections, central nervous system infections and bacteremia[9].

A. Cellulitis

Cellulitis due to Acinetobacter occurs in the presence of devitalized tissue or a foreign body, such as an intravenous catheter or a suture. The majority of soft tissue infections with Acinetobacter are nosocomially acquired; previous reports identified Acinetobacter as an important pathogen in soil-contaminated combat injuries in Vietnam[10].

Simply removing the intravenous catheter or suture, or debridement combined with local measures is usually adequate. Antibiotic therapy is not indicated in the absence of systemic signs of infection.

B. Respiratory Tract Infections

Acinetobacter can colonize the pharynx of normal ambulatory subjects; however, the highest rate of colonization occurs in patients with a tracheostomy[9]. Invasion of respiratory tract represents the largest percentage of Acinetobacter infections. Presumptively, infection occurs when pharyngeal colonization is followed by aspiration or direct inoculation of organisms via a suction catheter into a compromised pulmonary tree. Nosocomial outbreaks have been traced to the hands of nurses, respiratory care personnel and to colonized ventilator reservoirs[11]. Hematogenous spread to the lungs may also occur. Community-acquired pulmonary infections with Acinetobacter occur but are unusual.

Pneumonia associated with Acinetobacter is often multilobar and necrotizing. Diagnosis depends on a positive sputum culture, a diagnostic sputum Gram stain, increasing peripheral leukocyte count, new pulmonary infiltrate on chest roentgenogram and/or increasing sputum production. Tracheobronchitis may be present without lung findings. **More explicitly, mere isolation of Acinetobacter from the sputum is not diagnostic of a respiratory infection and therefore is not sufficient grounds to treat a patient.** There must be clinical evidence supporting an infectious pulmonary process.

Effective therapy for pneumonia requires appropriate antibiotics based on antibiotic sensitivities and pulmonary hygiene. Tracheobronchitis may resolve with pulmonary hygiene alone.

C. Central Nervous System Infections

Infections of the central nervous system (CNS) with Acinetobacter are distinctly rare in the ambulatory patient. They occur following neurosurgical procedures and/or in the neonatal intensive care unit. Both meningitis and brain abscess have been reported. The course may be indolent or fulminant including the Waterhouse-Friderichsen syndrome. Gram stain of infected CSF can cause diagnostic confusion as Acinetobacter may appear as small gram negative bacilli or diplococci depending on its rate of growth and the quality of the staining technique. More common organisms with these forms, *Haemophilus influenzae* and *Neiserria meningitidis*, respectively, may be suspected initially, resulting in a delay in effective therapy[12-14].

Early reports of therapy for Acinetobacter meningitis outlined the important role of intrathecal aminoglycoside in sterilizing the CNS[15]. With the development of broad-spectrum β-lactam antibiotics possessing excellent CNS penetration, intrathecal therapy became obsolete. However, therapeutic regimens must be flexible to adapt to the evolving microbial multiresistance.

Brain abscesses are treated with drainage and prolonged antibiotics.

D. Bacteremia

Acinetobacter bacteremia occurs secondarily to a respiratory, wound, urinary tract or intravenous catheter infection. The patient may be asymptomatic or in septic shock. Therapy depends on the source and symptomatology of the patient. The asymptomatic patient with bacteremia from an intravenous catheter requires catheter removal and observation. The more symptomatic patient will require antibiotics and possibly intensive life support. The prognosis of Acinetobacter bacteremia is determined by the patient's underlying illness. Those with polymicrobial sepsis do worse. Due to Acinetobacter's environmental presence, care must be taken in preparing the skin and blood culture bottle prior to blood culturing as "pseudobacteremia" may lead to unnecessary therapy[9].

V. ANTIBIOTIC RESISTANCE

Available therapeutic options have been expanded by

an appreciation of antimicrobial resistance mechanisms. In general, antibiotic resistance is due to a bacteria's ability to 1) produce enzymes that destroy or inactivate antibiotics, 2) alter its metabolic pathways to avoid intended antibiotic interference, or 3) prevent the antibiotic from entering the bacteria. Our usual efforts to deal with antibiotic resistance have been to devise new drugs that circumvent the existing resistance mechanisms. However, these drugs eventually succumb to the bacteria's acquisition of means to inactivate them. The ever-expanding effort to outwit bacteria results in expensive drug development and abandonment of previously useful antibiotics.

More recent efforts have focused on inactivating the bacteria's existing antibiotic resistance enzymes instead of avoiding them, thus rendering previously ineffective antibiotics useful again. For example, ampicillin can be given in combination with sulbactam, which is a "suicide" β-lactamase inhibitor. Sulbactam is attacked by and irreversibly bound to the ampicillin-inactivating enzyme (a β-lactamase), leaving this enzyme unable to attack the ampicillin. This allows the ampicillin to be effective again.

This conceptually simple approach allows numerous combinations of β-lactamase inhibitors and β-lactams to be used together. Drugs felt to be "obsolete" in treating many resistant bacteria are once again effective. The available combinations include: ampicillin/sulbactam, amoxicillin/clavulanic acid, ticarcillin/clavulanic acid, and several other combinations in clinical trials. Unfortunately, sulbactam (or related compounds) does not work against all β-lactam-inactivating enzymes. For example, a chromosomal β-lactamase produced by Klebsiella is inactivated by sulbactam, whereas plasmid mediated β-lactamases found in many multiresistant Klebsiella strains are not inactivated[16]. Despite these limitations, further investigations into the mechanisms of antibiotic resistance and means of counterattacking the microbes will allow other previously useful agents to be effective once again.

VI. CASE REPORT

Mr. P K, a 78 year old Chinese man presented with progressive numbness and weakness of the left foot in early 1988. In February 1988, he underwent a L4 partial laminectomy, a L5 complete laminectomy with root canal decompression and S1 root canal decompression. He had immediate improvement of his neurologic deficit, but by August 1989 his left leg symptoms recurred and were accompanied by urinary incontinence. Lumbar myelogram and Magnetic Resonance Imaging (MRI) revealed a large disc prolapse at L4/L5 with obstruction of the exit foramina. A L4 laminectomy with spinal canal exploration was performed in November 1989. A 5mm defect in the dura was inadvertently created. "Lyodura" was used to repair the rent.

His post-operative course was uneventful until the 12th post-operative day when a nontender seroma was noted in the operative incision. The following day the patient complained of headache and nausea. His temperature was 38.0° orally. The patient was found to have photophobia, meningismus, and a left sided neural hearing deficit. Lumbar puncture on that day produced lightly blood stained cerebrospinal fluid (CSF), (pressures not recorded), WBC packed, glucose level 0.8 mmol/L, total protein content of 7 G/dl, and a Gram stain with Gram negative bacilli noted. The peripheral leukocyte count was 9360 with 96% polymorphonuclear cells, serum glucose 5.3 mmol/L, serum creatinine 276 umol/L.

The patient was immediately begun on ceftriaxone and sulfadiazine. CSF bacterial culture isolated a heavy growth of *Acinetobacter calcoaceticus* var. *anitratus*, resistant to gentamicin, all penicillins, all cephalosporins, chloramphenicol, tetracycline, bactrim, aztreonam, imipenem, and moderately resistant to perfloxacin. The organism was found to be sensitive to ampicillin/sulbactam, netilmicin, and amikacin. On the 15th post-operative day, 3 gm of intravenous ampicillin/sulbactam every six hours and 200 mg of intravenous amikacin every twenty four hours was begun. The patient reported improvement in his headache within 48 hours and resolution of all symptoms of meninigitis within 96 hours. His hearing improved, the seroma resolved and he ambulated on postop day 25. He received fourteen days of ampicillin/sulbactam and amikacin. The patient was discharged ambulating with assistance on the 32nd post-operative day in good condition without recurrence of his seroma.

VI. DISCUSSION

The clinical response demonstrated by our patient dramatically documents the penetration of both sulbactam and ampicillin into the CSF, as the Acinetobacter isolate was resistant to ampicillin in the absence of sulbactam[17,18]. Applying the principle of combination therapy in serious infections with Acinetobacter, amikacin was presumptively given to prevent resistance development. It is unlikely the Acinetobacter responded to our patient's low dose of amikacin as only 15-25% of the serum level is achieved in the CSF.

VII. PREVENTION

The only effective means of preventing Acinetobacter colonizaton and infection is careful attention to hand washing by all hospital personnel, minimizing invasive monitoring, and careful epidemiologic follow-up of outbreaks to determine the common source.

VIII. SUMMARY

In conclusion, antibiotic-resistant *Acinetobacter calcoaceticus* is a frequent isolate from hospital clinical specimens. Patient colonization occurs via hospital personnel and equipment. Awareness of the means of spread and the implications of isolating this organism are essential for the appropriate interpretation of culture results. Acinetobacter acts as a pathogen in patients with compromised defense barriers. Clinical syndromes may range from benign to lethal. Therapy is dictated by the severity of the patient's condition and may entail only local measures. Colonized patients require no specific therapy. Systemic therapy is complicated by the multiresistant nature of these organisms. Understanding how to minimize breaching host defense, the means to counteract antimicrobial resistance and preventing nosocomial spread will advance our approach to this common problem.

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