as GacSA was described as important in regulating *A. baumannii* biofilms, motility, growth in human serum, and virulence in a mammalian infection model.

New model systems for the study of *A. baumannii* infection, including both nonmammalian (invertebrate) and mammalian models, have been described. Furthermore, the use of *A. baumannii* transposon-generated mutant libraries to screen for mutants with attenuated growth in human biologic fluids (serum and ascites fluid) has allowed the identification of new virulence mechanisms. These include phospholipase D; capsule production mediated by *ptk* and *epsA*; penicillin-binding protein 7/8 encoded by the *pbpG* gene; and a glycosyltransferase important for LPS biosynthesis encoded by the *lpsB* gene.

The LPS of *A. baumannii* appears to play a significant role in eliciting host responses. In studies with knockout mice, Toll-like receptor 4 and CD14 were shown to be important in host recognition, signaling, and cytokine production in response to *A. baumannii*. Humoral responses targeting iron-regulated outer-membrane proteins and the O-polysaccharide component of LPS also have been described.

APPROACH TO THE PATIENT: *Acinetobacter* Infection

Acinetobacter must be considered in the differential diagnosis of hospital-acquired pneumonia, central line–associated bloodstream infection, posttraumatic wound infection in military personnel, and postneurosurgical meningitis.

CLINICAL MANIFESTATIONS

Pneumonia It may be difficult to distinguish between upper-airway colonization with *A. baumannii* and hospital-acquired pneumonia. An estimated 5–10% of cases of ventilator-associated pneumonia are due to *A. baumannii*, although much regional variation exists. Typically, patients with *A. baumannii* ventilator-associated pneumonia have had a prolonged stay in an ICU; in outbreak situations, however, patients may acquire the infection within days of arrival in an ICU.

Community-acquired pneumonia due to *A. baumannii* has been described in tropical regions of Australia and Asia. The disease typically occurs during the "wet" season among people with a history of alcohol abuse. Infection may result in fulminant pneumonia requiring admission to an ICU, with a mortality rate of ~50%.

Bloodstream Infection Although *A. baumannii* accounts for only ~1–2% of nosocomial bloodstream infections, crude mortality rates from these infections may be as high as 40%. Sources of bloodstream infection are typically a central line or underlying pneumonia, UTI, or wound infection.

Traumatic Battlefield and Other Wounds *A. baumannii* is a well-known pathogen in burn units. This organism is commonly isolated from wounds of combat casualties; it was the most commonly isolated organism in one assessment of combat victims with open tibial fractures but did not appear to contribute directly to persistent nonunion or the need for amputation.

Meningitis *A. baumannii* may cause meningitis following neurosurgical procedures. Patients typically have an external ventricular drain in situ.

Urinary Tract Infection *A. baumannii* is an occasional cause of catheter-associated UTI. It is highly unusual for this organism to cause uncomplicated UTI in healthy women.

Other Clinical Manifestations A small number of case reports describe *Acinetobacter* prosthetic-valve endocarditis and endophthalmitis/keratitis. The latter is sometimes related to contact lens use or eye surgery.

DIAGNOSIS

Acinetobacter infection should be suspected when plump coccobacilli are seen in Gram's-stained respiratory tract secretions, blood cultures, or cerebrospinal fluid. Sometimes the organisms are difficult to de-stain. Given their small size, they may be misidentified as either gram-negative or gram-positive cocci.

TREATMENT *ACINETOBACTER* INFECTION (TABLE 187-1)

Treatment is hampered by the remarkable ability of *A. baumannii* to upregulate or acquire antibiotic resistance determinants. The most prominent example is that of β-lactamases, including those capable of inactivating carbapenems, cephalosporins, and penicillins. These enzymes, which include the OXA-type β-lactamases (e.g., OXA-23), the metallo-β-lactamases (e.g., NDM), and rarely KPC-type carbapenemases, are typically resistant to currently available β-lactamase inhibitors such as clavulanate or tazobactam. Plasmids that harbor genes encoding these β-lactamases may also harbor genes encoding resistance to aminoglycosides and sulfur antibiotics. The end result is that carbapenem-resistant *A. baumannii* may become truly multidrug resistant.

Selection of empirical antibiotic therapy when *A. baumannii* is suspected is challenging and must rely on a knowledge of local epidemiology. Receipt of prompt, effective antibiotic therapy is the goal. Given the diversity of resistance mechanisms in *A. baumannii*, definitive therapy should be based on the results of antimicrobial susceptibility testing. Carbapenems (imipenem, meropenem, and doripenem but not ertapenem) have long been thought of as the agents of choice for serious *A. baumannii* infections. However, the clinical utility of carbapenems is now widely jeopardized by the production of carbapenemases, as described above. Sulbactam may be an alternative to carbapenems. Unlike other β-lactamase inhibitors (e.g., clavulanic acid and tazobactam), sulbactam has intrinsic activity against *Acinetobacter*; this activity is mediated by the drug's binding to penicillin-binding protein 2 rather than by its ability to inhibit β-lactamases. Sulbactam is commercially available in a combined formulation with either ampicillin or cefoperazone and may also be available as a single agent in some countries. Despite the absence of randomized clinical trials, sulbactam seems to be equivalent to carbapenems in clinical effectiveness against susceptible strains.

Therapy for carbapenem-resistant *A. baumannii* is particularly problematic. The only currently available choices are polymyxins (colistin and polymyxin B) and tigecycline. Neither option is perfect. Polymyxins may be nephrotoxic and neurotoxic. Definition of the optimal dose and schedule for administration of polymyxins to patients in vulnerable groups (e.g., those requiring renal replacement therapy) remains challenging, and emergence of resistance in association with monotherapy is a concern. Conventional doses of tigecycline may not result in serum concentrations adequate to treat bloodstream infections. Resistance of *A. baumannii* to tigecycline may develop during treatment with this drug.

As a consequence of these issues with the polymyxins and tigecycline, combination therapy is now favored for carbapenem-resistant *Acinetobacter*. However, in a randomized controlled trial, 30-day mortality was not reduced by the addition of rifampin to colistin. Nevertheless, a significant increase in microbiologic eradication was observed in the colistin plus rifampin arm over that attained with

TABLE 187-1 TREATMENT OPTIONS FOR *ACINETOBACTER* INFECTIONS

Antibiotic	Comments
Sulbactam	Intrinsic activity against *Acinetobacter,* not linked to β-lactamase inhibition
Trimethoprim-sulfamethoxazole	May be an option for urinary tract infection or wound infection
Meropenem	Carbapenem resistance now widespread
Amikacin	May be an option for carbapenem-resistant strains
Tigecycline	May be an option for carbapenem-resistant strains but inappropriate for urinary tract infection, bloodstream infection, or meningitis
Colistin or polymyxin B	May be an option for carbapenem-resistant strains, but pharmacokinetics not yet well understood