S. aureus infections become infected with a strain that is already a part of their own commensal flora. Breaches of the skin or mucosal membrane allow *S. aureus* to initiate infection.

Some diseases increase the risk of *S. aureus* infection; diabetes, for example, combines an increased rate of *S. aureus* colonization and the use of injectable insulin with the possibility of impaired leukocyte function. Individuals with congenital or acquired qualitative or quantitative defects of polymorphonuclear leukocytes (PMNs) are at increased risk of *S. aureus* infections; this group includes neutropenic patients (e.g., those receiving chemotherapeutic agents), those with chronic granulomatous disease, and those with Job's or Chédiak-Higashi syndrome. Other groups at risk include individuals with end-stage renal disease, HIV infection, skin abnormalities, or prosthetic devices.

S. aureus is a leading cause of health care–associated infections (Chap. 168). It is the most common cause of surgical wound infections and is second only to CoNS as a cause of primary bacteremia. These isolates are generally resistant to multiple antibiotics; thus available therapeutic options are limited. In the community, *S. aureus* remains an important cause of skin and soft tissue infections, respiratory infections, and (among injection drug users) infective endocarditis. The increasing use of home infusion therapy is another cause of community-acquired staphylococcal infections.

In the past two decades, there has been a dramatic change in the epidemiology of infections due to methicillin-resistant *S. aureus* (MRSA). In addition to its major role as a nosocomial pathogen, MRSA has become an established community-based pathogen. Numerous outbreaks of community-associated MRSA (CA-MRSA) infections have been reported in both rural and urban settings in widely separated regions throughout the world. The outbreaks have occurred among such diverse groups as children, prisoners, athletes, Native Americans, and drug users. Risk factors common to these outbreaks include poor hygienic conditions, close contact, contaminated material, and damaged skin. These infections have been caused by a limited number of MRSA strains. In the United States, strain USA300 (defined by pulsed-field gel electrophoresis) has been the predominant clone. In other geographic regions of the world, different strains of CA-MRSA have been responsible for these community-based outbreaks. Although the majority of infections caused by these strains have involved the skin and soft tissue, 5–10% have been invasive and potentially life-threatening. CA-MRSA strains have also been responsible for an increasing number of nosocomial infections. Of concern has been the apparent capacity of CA-MRSA to cause disease in immunocompetent individuals.

PATHOGENESIS

General Concepts *S. aureus* is a pyogenic pathogen known for its capacity to induce abscess formation at sites of both local and metastatic infections. This classic pathologic response to *S. aureus* defines the framework within which the infection will progress. The bacteria elicit an inflammatory response characterized by an initial intense infiltration of PMNs and a subsequent infiltration of macrophages and fibroblasts. Either the host cellular response (including the deposition of fibrin and collagen) contains the infection, or infection spreads to the adjoining tissue or the bloodstream.

In toxin-mediated staphylococcal disease, infection is not invariably present. For example, once toxin has been elaborated into food, staphylococcal food poisoning can develop in the absence of viable bacteria. In staphylococcal toxic shock syndrome (TSS), conditions allowing toxin elaboration at colonization sites (e.g., the presence of a superabsorbent tampon) suffice for initiation of clinical illness.

The *S. aureus* Genome The complete genomes of numerous strains of *S. aureus* have now been fully sequenced. Among the interesting revelations are (1) the high degree of nucleotide sequence similarity of the core genomes of different strains; (2) acquisition of a relatively large amount of genetic information by horizontal transfer from other bacterial species; and (3) the presence of unique "pathogenicity" or "genomic" islands—mobile genetic elements that contain clusters of enterotoxin and exotoxin genes and/or antimicrobial resistance determinants. Among the genes in these islands are those carrying *mecA*, the gene responsible for methicillin resistance. Methicillin resistance–containing islands have been designated staphylococcal cassette chromosome *mec* (SCC*mec*) types and range in size from ~20 to 60 kb. To date, 11 SCC*mec* types have been identified. Among the more common types, types 1–3 are traditionally associated with nosocomial MRSA isolates, whereas types 4–6 have been associated with the epidemic CA-MRSA strains.

A limited number of MRSA clones have been responsible for most community- and hospital-associated infections worldwide. A comparison of these strains with those from earlier outbreaks (e.g., the phage 80/81 strains from the 1950s) has revealed preservation of the nucleotide sequence over time. This observation suggests that these strains possess determinants that facilitate survival and spread.

Regulation of Virulence Gene Expression In both toxin-mediated and non-toxin-mediated diseases due to *S. aureus*, the expression of virulence determinants associated with infection depends on a series of regulatory genes (e.g., accessory gene regulator [*agr*] and staphylococcal accessory regulator [*sar*]) that coordinately control the expression of many virulence genes. The regulatory gene *agr* is part of a quorum-sensing signal transduction pathway that senses and responds to bacterial density. Staphylococcal surface proteins are synthesized during the bacterial exponential growth phase in vitro. In contrast, many secreted proteins, such as α toxin, the enterotoxins, and assorted enzymes, are released during the postexponential growth phase in response to transcription of the effector molecule of *agr*, RNAIII.

It has been hypothesized that these regulatory genes serve a similar function in vivo. Successful invasion requires the sequential expression of these different bacterial elements. Bacterial adhesins are needed to initiate colonization of host tissue surfaces. The subsequent release of various enzymes enables the colony to obtain nutritional support and permits bacteria to spread to adjacent tissues. Studies with strains in which these regulatory genes are inactivated show reduced virulence in several animal models of *S. aureus* infection.

Pathogenesis of Invasive *S. aureus* Infection Staphylococci are opportunists. For these organisms to invade the host and cause infection, some or all of the following steps are necessary: contamination and colonization of host tissue surfaces, breach of cutaneous or mucosal barriers, establishment of a localized infection, invasion, evasion of the host response, and metastatic spread. Colonizing strains or strains transferred from other individuals are introduced into damaged skin, a wound, or the bloodstream. Recurrences of *S. aureus* infections are common, apparently because of the capacity of these pathogens to survive, to persist in a quiescent state in various tissues, and then to cause recrudescent infections when suitable conditions arise.

***S. AUREUS* COLONIZATION OF BODY SURFACES** The anterior nares is one of the primary sites of staphylococcal colonization in humans. Colonization appears to involve the attachment of *S. aureus* to keratinized epithelial cells of the anterior nares. Other factors that may contribute to colonization include the influence of other resident nasal flora and their bacterial density, host factors, and nasal mucosal damage (e.g., that resulting from inhalational drug use). Other colonized body sites, such as damaged skin, the groin, and the oropharynx, may be particularly important reservoirs for CA-MRSA strains.

INOCULATION AND COLONIZATION OF TISSUE SURFACES Staphylococci may be introduced into tissue as a result of minor abrasions, administration of medications such as insulin, or establishment of IV access with catheters. After their introduction into a tissue site, bacteria replicate and colonize the host tissue surface. A family of structurally related *S. aureus* surface proteins referred to as MSCRAMMs (microbial surface components recognizing adhesive matrix molecules) plays an important role in mediating adherence to these sites. By adhering to exposed matrix molecules (e.g., fibrinogen, fibronectin), MSCRAMMs such as clumping factor and collagen-binding protein enable the bacteria to colonize different tissue surfaces; these proteins contribute to