Coagulase-Negative Staphylococci

INTRODUCTION

The clinical importance of coagulase-positive staphylococci is well-known. In fact, *Staphylococcus aureus* is so often considered a pathogen that few laboratories appreciate that up to 25% of these strains isolated from blood cultures are actually contaminants from skin flora. Conversely, coagulase-negative staphylococci have so long been considered an environmental contaminant that the pathogenic significance of such an isolate may go unrecognized. Moreover, since 1960 there has been a marked increase in the incidence of infections caused by coagulase-negative staphylococci, paralleling the increase in numbers of compromised hosts. These staphylococci are particularly important in nosocomial infections. Therefore, it seems pertinent to review both the speciation and the infections caused by these organisms.

BASIC PRINCIPLES

Speciation

Over the years, it has been common practice in the clinical microbiology laboratory to divide staphylococci into two species based on the presence of coagulase. Coagulase-positive staphylococci are considered synonymous with *S. aureus*, and coagulase-negative staphylococci are usually indicative of *S. albus* or *S. epidermidis*. Some laboratories utilize a novobiocin disc to identify *S. saprophyticus* by its resistance to this antibiotic. However, such simplification is no longer relevant. Although several biotyping schemes have been developed, that of Kloos and Schleifer has proved the most satisfactory and is currently the most widely accepted. Using this scheme, Kloos and Schleifer have demonstrated the presence of nine separate species of coagulase-negative staphylococci. These nine species of coagulase-negative staphylococci are listed in Table 1 in decreasing order of pathogenicity to man as demonstrated by speciation of clinical isolates.

Speciation is accomplished by a wide range of biochemical tests. These tests are tedious for clinical microbiology laboratories to perform routinely. Moreover, cell wall analysis may be required for complete separation of some species. Thus, most laboratories do not bother to speciate coagulase-negative staphylococci. Until this is done, the pathogenic potential of these organisms will continue to be misjudged, and these isolates may be ignored as contaminants.

There are cogent arguments advocating speciation of these strains to learn more about their pathogenicities. There may also be epidemiological value in such speciation. For example, speciation could be useful in determination of sources (i.e., exogenous or endogenous) of contaminating organisms that may be introduced during the insertion of prosthetic devices. Obviously, any such speciation needs to be closely coordinated with the clinical circumstances associated with isolation of the organisms.

In the future, it may be easier to perform such speciation routinely in the clinical microbiology laboratory. Because of increased interest in these opportunistic pathogens, a typing system based on biochemical criteria is now available commercially. This test system comprises 10 biochemical tests: production of phosphatase; hydrolysis of urea; production of beta-glucosidase; fermentation of mannose, mannitol, trehalose, salicin; production of beta-glucuronidase; production of arginine dihydrolase; and production of beta-galactosidase. It is a miniaturized system and may prove useful in the routine identification of clinical isolates of coagulase-negative staphylococci.

Phage Typing

Another potentially useful procedure for epidemiologic surveillance of coagulase-negative staphylococci is phage typing. Although, to date, this procedure has been neither

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*Staph-ident, Analytab Product, Plainview, NY.*
specific enough nor readily available, various workers have developed pools of lysogenic phages that may eventually form an internationally-recognized standard for typing.

Pathogenicity

Coagulase-negative staphylococci, like coagulase-positive strains, are frequent inhabitants of skin and mucosal surfaces. These strains have been thought to produce neither coagulase nor the wide variety of extracellular enzymes formed by S. aureus. The lack of these enzymes may account for the relatively decreased pathogenicity of coagulase-negative staphylococci as compared with S. aureus. However, Gemmell and coworkers have shown that coagulase-negative staphylococci isolated from human infections do produce a limited number of toxins and enzymes. These investigators have developed a colony-overlay technique that utilizes a semisolid agar overlying a monolayer of skin fibroblasts, to assay the toxigenicity of these strains. They found that cytopathogenic strains were primarily epidermidis, saprophyticus, and haemolyticus biotypes. They also noted particularly good correlation between a strain’s ability to cause cell damage and to produce delta-hemolysin in culture. This ability to elaborate exotoxins is probably related to these organisms’ capacities to cause infection.

INFECTIONS CAUSED BY COAGULASE-NEGATIVE STAPHYLOCOCCI

Skin Infections

Because of their presence on the skin, coagulase-negative staphylococci are often involved in minor skin infections. Abscesses following injury to the skin by trauma or surgical procedures are such infections; deeper infection may also occur, such as that seen with sternal osteomyelitis following cardiac surgery. As might be expected, coagulase-negative staphylococci can cause infections associated with intravenous use. Unfortunately, they are also commonly found as colonizers of the IV catheter tips. It is impossible to differentiate between infection and colonization if the IV catheter is cultured in broth. Instead, it is necessary to use the technique developed by Maki, where the catheter tip is rolled across the surface of an agar plate. Growth of more than 15 colonies indicates infection.

Prosthetic Device Infections

Coagulase-negative staphylococci are frequently implicated as etiological agents in a large number of infections involving prosthetic devices. Such devices include prosthetic heart valves, cerebrospinal fluid shunts (Spitz-Holter valves), hemodialysis and peritoneal dialysis shunts, dacron vascular grafts, and joint prostheses. A well-known example of such infections are those involving cerebrospinal fluid shunts; the infection rates vary from 4% to 27% and markedly increase morbidity and mortality. Coagulase-negative staphylococci are responsible for the majority of these infections. One study has demonstrated that some strains of coagulase-negative staphylococci produce a mucoid substance that facilitates adherence of the organism to synthetic materials. Hence, these organisms may be particularly able to first colonize and later infect a prosthetic device.

Most of the coagulase-negative staphylococci isolated from prosthetic infections are epidermidis strains; the exact method of entry is unknown, although it may result from perisurgical contamination of skin isolates from either the patient or surgical personnel. There has been a high incidence of coagulase-negative staphylococci environmental contamination in operating rooms. In one study, coagulase-negative staphylococci were recovered from 50% to 80% of positive cultures from both the operating room air and hip wound cultures done during total hip replacement surgery.

Other mechanisms of entry may exist. Vascular infections on prosthetic devices, such as heart valves or vascular grafts, may be a result of transient bacteremia. Another possible source of prosthetic heart valve infections is the frequent colonization of postoperative IV catheters by coagulase-negative staphylococci from skin. These isolates, when speciated, are not always S. epidermidis. Their exact role in infection of prosthetic heart valves remains to be determined.

Urinary Tract Infections

The occurrence of bacteriuria due to coagulase-negative staphylococci was first described in the late 1960s. Infection rates due to these organisms vary from 5% to 15% depending on the population examined. Unlike E. coli infections, infections due to staphylococci have a tendency to resolve spontaneously and have a lower recurrence rate. These infections have now been described in all age groups and in both hospitalized and nonhospitalized persons. Most of the isolates associated with urinary tract infections have been saprophyticus strains. Of the coagulase-negative staphylococci, only S. saprophyticus has been shown to have a marked ability to attach to urethral cells. Thus, these organisms may be more able to colonize and produce infection in the urethra and bladder. In fact, because of this ability to attach to urethral cells, S. saprophyticus has also been suggested as an etiological agent of nongonococcal urethritis.

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COMMENTS: pHisoHex is a bacteriostatic cleansing agent. It cleanses the skin thoroughly and has bacteriostatic action against staphylococci and other gram-positive bacteria. Cumulative bacteriostatic action develops with repeated use. This antibacterial residue is resistant to removal by many solvents, soaps, and detergents for several days. pHisoHex has the same slight acidity as normal skin (pH value 5.5 to 6.0). 

OTHER INFECTIONS

Coagulase-negative staphylococci have been isolated from a variety of other infections, suggesting that their role is not yet fully appreciated. For example, these staphylococci have been implicated in eye infections including endophthalmitis. An outbreak of ophthalmia neonatorum in a newborn nursery due to coagulase-negative staphylococci was reported. Isolates are also being reported from infections in neonates, cancer patients, and others with compromised defense mechanisms. Even food poisoning due to these coagulase-negative strains may be seen; one outbreak of foodborne gastroenteritis was traced to an enterotoxin-producing strain of coagulase-negative staphylococci from crusted impetiginous lesions on a cook's hands. In summary, it is becoming clear that many infections in humans can be caused by various coagulase-negative strains of staphylococci. Thus, the staphylococci may represent a spectrum of organisms ranging from pathogenic S. aureus to commensal S. hominis. 

RESISTANCE TO ANTIBIOTICS

There are indications that those strains of coagulase-negative staphylococci that cause clinical infections often have a high level of resistance. This is particularly true for those strains that cause prosthetic valve endocarditis. Methicillin and cephalothin resistance is quite common. This resistance may be mediated by plasmids that can be transferred by transformation, transduction, and possibly other mechanisms. There is epidemiologic evidence of naturally-occurring transfer of plasmids by both S. epidermidis and S. aureus. Skin isolates of S. epidermidis can rapidly develop resistance to multiple antibiotics when a person is hospitalized.

As with methicillin-resistant S. aureus, there can be considerable difficulty correlating the results of in vitro susceptibility testing with clinical cures. Both extensive clinical experience and animal models have demonstrated this problem. Vancomycin has been found to be the most effective treatment for infections caused by both methicillin-resistant S. aureus and resistant strains of S. epidermidis. 

SUMMARY

It is clear that the status of coagulase-negative staphylococci in clinical microbiology has changed dramatically; what were thought to be merely skin contaminants are now realized as significant nosocomial pathogens. More work is needed to delineate the various subspecies that are apt to be pathogenic when isolated from clinical specimens. Finally, it must be remembered that coagulase-negative staphylococci may still be isolated as contaminants. It is only through effective dialogue between clinicians and the laboratory that the significance of such isolates can be determined for a particular patient.

Kenneth E. Aldridge, Ph.D.
Division of Infectious Diseases
Department of Medicine
LSU Medical Center
New Orleans, Louisiana

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