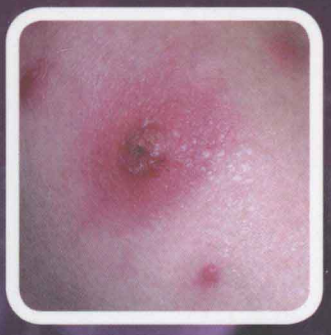
Second Edition

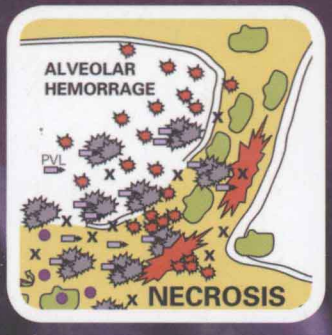
Staphylococci in Human Disease

EDITED BY

Kent B. Crossley · Kimberly K. Jefferson

Gordon L. Archer · Vance G. Fowler Jr





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SECOND EDITION

WILEY-BLACKWELL
A John Wiley & Sons, Ltd., Publication

This edition first published 2009, © 2009 by Blackwell Publishing Ltd

Blackwell Publishing was acquired by John Wiley & Sons in February 2007.
Blackwell's publishing program has been merged with Wiley's global Scientific, Technical and Medical business to form Wiley-Blackwell.

Registered office: John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial offices: 9600 Garsington Road, Oxford, OX4 2DQ, UK
The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK
111 River Street, Hoboken, NJ 07030-5774, USA

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Library of Congress Cataloging-in-Publication Data
Staphylococci in human disease / edited by Kent B. Crossley . . . [*et al.*]. – 2nd ed.
p. ; cm.
Includes bibliographical references and index.
ISBN: 978-1-4051-6332-3
1. Staphylococcal infections. I. Crossley, Kent B.
[DNLM: 1. Staphylococcus–pathogenicity. 2. Staphylococcal Infections.
QW 142.5.C6 S7935 2010]
QR201.S68S84 2010
616.9'297–dc22

2009004429

A catalogue record for this book is available from the British Library.

Set in 9.25/12pt Palatino by Graphicraft Limited, Hong Kong
Printed in and bound in Singapore by Fabulous Printers Pte Ltd

1 2009

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Preface to the Second Edition

In the preface to the original edition of this book, written over a decade ago, we noted that there were three reasons to plan and edit a book about staphylococci and staphylococcal infection. These same reasons are even more important today than they were in 1997.

Firstly, the significance of staphylococcal infection has continued to increase. When the original edition was published, methicillin-resistant staphylococci were relatively uncommon. That has changed dramatically in the last decade. In 2005, 19 000 deaths in the USA resulted from methicillin-resistant *Staphylococcus aureus* (MRSA) infection. This number exceeded both HIV-AIDS and homicide as causes of mortality. Community-acquired MRSA infections, almost unknown in 1997, have become a substantial problem in subsequent years. Nothing we have read suggests to us that mortality from staphylococcal infection is lower than it was in 1997 or that newer antistaphylococcal antibiotics are likely to result in more favorable outcomes. Staphylococci remain the most important cause of nosocomial infections in the USA and MRSA has become the most common cause of skin and soft tissue infection in the community.

Secondly, the volume of information about staphylococci and staphylococcal infection has grown at a rapid rate. In 1997, there were 2283 papers indexed by the National Library of Medicine under the headings "staphylococci" or "staphylococcal infection." In 2008, there were 12 330 papers in these categories. This extraordinary amount of information demands assessment by skilled and critical authors and editors. We have an outstanding group of authors who have carefully sifted through this information and provided succinct evaluations of their part of this enormous collection of literature.

Finally, no other book like this has been published since our first edition. The books about staphylococci that have been published in the last decade have focused on laboratory science or have been symposia proceedings.

Our goal here – as with the first edition – is to provide a comprehensive review of both basic and clinical science about staphylococci. This volume should be of value to both researchers and clinicians. We hope you find it useful.

Kent B. Crossley
Kimberly K. Jefferson
Gordon L. Archer
Vance G. Fowler, Jr.
September 2009

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Section I
The Organisms

Biology and Taxonomy

Chapter 1
The Biology of Staphylococci

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Historical perspective of the isolation and characterization of the staphylococci

The staphylococci make up the family of Gram-positive cocci, Staphylococcaceae, which is in the order Bacillales. The term "staphylococcus" was synthesized from the Greek word *staphyle*, meaning bunch of grapes, for their ability to form microscopic grape-like clusters, and the term "coccus," meaning grain or berry. *Staphylococcus aureus* was one of the first bacterial pathogens identified, and causes a very broad range of infections including impetigo, folliculitis, superficial and deep skin abscesses, wound infections, osteomyelitis, suppurative arthritis, pneumonia, pleural emphysema, meningitis, septicemia and endocarditis, toxic shock syndrome, scalded skin syndrome, and food poisoning [1].

Koch first differentiated Gram-positive cocci in 1878 and recognized that different diseases such as abscesses correlated with the presence of clusters of Gram-positive cocci. Shortly thereafter, in 1884, Rosenbach differentiated species of staphylococci on the basis of colonial pigmentation, whereby the most pathogenic species formed a golden pigment and less pathogenic staphylococci formed white colonies called *S. albus*, now *S. epidermidis*. Also included in the *S. albus* strains were many other coagulase-negative staphylococci that fail to form pigment. Alexander Ogston, in 1880, found "a cluster forming coccus was the cause of certain pyogenous abscesses in man." When Ogston injected the pus from humans containing staphylococci into mice, it produced abscesses; however, when the pus was heated or treated with phenol, it failed to produce abscesses. In 1882, Ogston named the organism staphylococcus. Pasteur had reached similar conclusions at approximately the same time. Coagulase testing later provided a more certain classification of staphylococci than pigment production, wherein a positive coagulase test, which confirmed the identity of *S. aureus*, correlated much better with pathogenicity.

Another common human pathogen is *S. saprophyticus*, which produces urinary tract infections in young women [2]. *Staphylococcus haemolyticus* is somewhat less common, but is important because it can be highly antibiotic resistant even to glycopeptides and linezolid [3]. Many other coagulase-negative strains (41 species identified at present) such as *S. schleiferi* and *S. lugdunesis* have been described, and they can produce a variety of nosocomial infections (reviewed by von Eiff *et al.* [4,5]).

Morphology

Staphylococci have a diameter of 0.7–1.2 μm and a Gram-positive cell wall (Figure 1.1). Division planes occur at right angles and the cocci separate slowly, hence tetrads are frequently found. Clustering of cocci is promoted by growth on solid medium. On occasion, the clusters may be asymmetrical.

Microbiological differentiation of staphylococci

Growth under various conditions

Staphylococci are facultative anaerobes that grow most rapidly under aerobic conditions and in the presence of CO_2. Colonies of *S. aureus* are β-hemolytic due to the production of several hemolysins: α-toxin, β-toxin, γ-toxin, and δ-toxin. Some *S. epidermidis* strains are β-hemolytic due to the production of δ-toxin [6]. Pigmentation is more pronounced after 24 hours and when held at room temperature, or in media enriched with acetate or glycerol monophosphate [7,8]. The pigments are carotenoids, whose biosynthetic pathway has recently been identified in *S. aureus* [9]. Pigment is not produced under anaerobic

Staphylococci in Human Disease, 2nd edition. Edited by Kent B. Crossley, Kimberly K. Jefferson, Gordon Archer, Vance G. Fowler, Jr.
 ISBN 978-14051-6332-3.

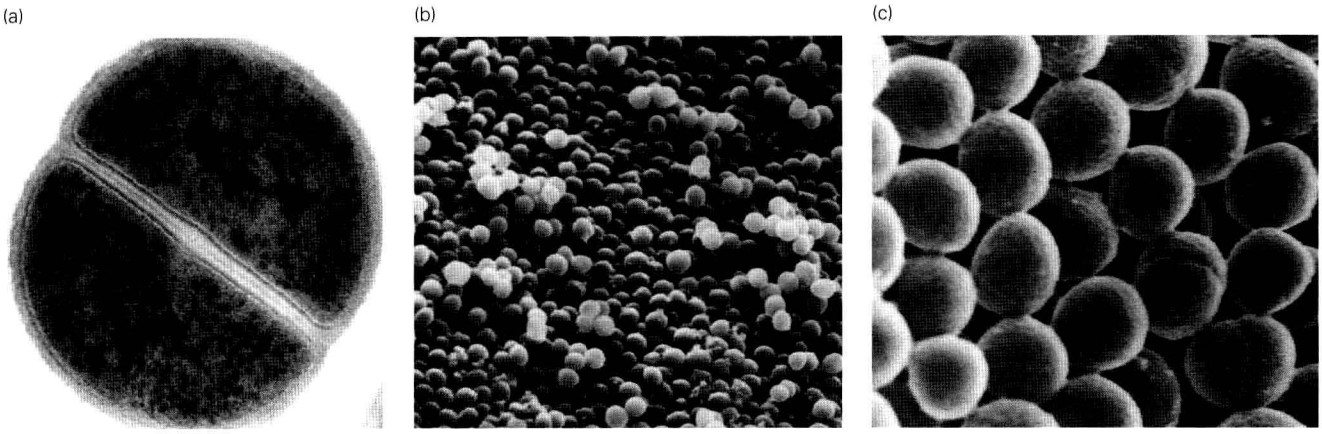

Figure 1.1 (a) Transmission electron microscopy at 126 700× magnification of *S. aureus* cells displaying cell separation by a cross-wall surrounding a highly contrasting splitting system. Scanning electron microscopy of *S. aureus* cells at (b) low (6700×) and (c) high (35 000×) magnification. Reproduced with permission from Kahl BC, Belling G, Reichelt R, Herrmann M, Proctor RA, Peters G. Thymidine-dependent small-colony variants of Staphylococcus aureus exhibit gross morphological and ultrastructural changes consistent with impaired cell separation. *J Clin Microbiol* 2003;41(1):410–3.

conditions or by small colony variants [10]. The formation of pigments is dependent on the stress sigma factor, σ^B [11]. A few *S. aureus* strains produce abundant exopolysaccharide (e.g., Smith strain, which produces a mucoid colony); however, most strains produce only a microcapsule and the colonies appear non-mucoid [12]. When encountered in clinical strains, the most frequent *S. aureus* serotypes are capsule types 5 and 8 [12]. In contrast to *S. aureus*, most clinical *S. epidermidis* isolates produce more exopolysaccharide.

Staphylococci can grow in a wide pH range (4.8–9.4), resist drying, and can survive at temperature extremes as high as 60°C for 30 min. In addition, *S. aureus* grows in high-salt medium due to the production of osmoprotectants [13], and can tolerate 7.5–10% NaCl. The ability of *S. aureus* to ferment mannitol is the basis for differentiating it from *S. epidermidis* and *S. saprophyticus*. When grown on mannitol salt agar, fermentation of mannitol produces a yellow zone around the colony. In addition to mannitol, *S. aureus* can metabolize glucose, xylose, lactose, sucrose, maltose, and glycerol. Further differentiation of staphylococci can be achieved by growth in the presence of novobiocin. *Staphylococcus saprophyticus* [14] and *S. xylosus* [5] are intrinsically resistant to novobiocin because their version of the DNA gyrase B enzyme does not bind novobiocin whereas other coagulase-negative staphylococci such as *S. epidermidis*, *S. haemolyticus*, *S. hominis*, *S. lugdunensis*, and *S. schleiferi* are novobiocin susceptible [5].

Special media

Several nonroutine agars are used to study *S. aureus* enzymes. Lipases produce clearing on egg yolk agar, especially when grown under anaerobic conditions [15]. *Staphylococcus aureus* protease activity can be monitored on casein agar plates, where protease-positive strains produce clearing of the agar [16]. When V8 protease (encoded by *sspA*) is present, it produces a zone of white precipitates around the colony [16]. Finally, tellurite is often added to growth media for the selection of *Corynebacterium diphtheriae* in pharyngeal specimens; *S. aureus* may be found in the pharyngeal specimens and can grow in the presence of tellurite, producing gray-black colonies that allow it to be confused with *C. diphtheriae*.

Other methods for differentiation of staphylococci

Staphylococci can be differentiated from micrococcus species based on their susceptibility to lysis by lysostaphin [17]. Lysostaphin is a metalloendopeptidase that targets the pentaglycine bridge of peptidoglycan [18].

Phenol soluble modulins have been associated with more severe staphylococcal infections and require specialized chromatography and mass spectrometry for identification and quantification [19].

While polymerase chain reaction (PCR) testing is not yet routine practice, its use is becoming more widely available in clinical as well as research laboratories. One of the most reliable PCR tests for *S. aureus* [20] detects the presence of the thermonuclease gene *nuc* [20–22]. PCR can also be used to test for the presence of genes encoding Panton-Valentine leukocidin (PVL), which is indicative of strains of community-acquired methicillin-resistant *S. aureus* (CA-MRSA) [23].

Colonization with staphylococci

Nasal carriage of *S. aureus* is persistently present in 30% of people and transiently found in 70% of people; conversely, 30% of people resist nasal colonization [4,24]. A higher incidence rate of nasal carriage of CA-MRSA has also been associated with individuals having frequent contact with

cats, dogs, pigs, and horses, suggesting that animals can be vectors in the spread of CA-MRSA [25–28]. *Staphylococcus aureus* reportedly adheres to nasal mucosa through several surface protein adhesins, including SasG, clumping factor, and fibronectin-binding protein [29–32]. Indeed, the staphylococci have a large array of surface proteins and carbohydrates that enable binding to a broad range of host tissues, including platelets, epithelial cells, endothelial cells, and host intercellular matrix proteins [33]. More detailed information concerning staphylococcal adherence to host tissues is covered in Chapter 7.

CA-MRSA demonstrate distinctive patterns of colonization, as they may be found solely in the throat or on the skin but are culture negative in the nares [34,35]. For this reason, testing individuals for colonization by nasal culture alone may not be sufficient for detection of CA-MRSA colonization.

Several recent studies suggest that streptococci may compete with CA-MRSA for colonization of mucosal surfaces. In a study by Chen *et al.* [36], it was observed that 17% of pregnant women were found to be vaginally colonized with *S. aureus* but only 0.5% were colonized by MRSA. Colonization of the vagina with *S. aureus* was associated with an 11-fold increased risk of postpartum fever. Interestingly, patients vaginally colonized with CA-MRSA were 12.5 times less likely to carry group B streptococci. In contrast, when methicillin-sensitive *S. aureus* (MSSA)-colonized patients were compared with patients who were not *S. aureus* colonized, the MSSA patients were 4.5 times more likely to carry group B streptococci [37]. These data suggest that group B streptococci are especially important for competing with CA-MRSA for colonization of vaginal mucosa. Similarly, on the oropharyngeal mucosal surfaces, *Streptococcus pneumoniae* may be important for preventing oral colonization by CA-MRSA. Children carrying *Streptococcus pneumoniae* are less likely to carry *S. aureus* [38], and pneumococcal vaccination increases *S. aureus* colonization [39,40]. While the heptavalent conjugate vaccine was not licensed for use in children in the USA until 2000 and in Europe until 2001, the first report of oral colonization by CA-MRSA was in 1998 [41]. Nevertheless, vaccination and subsequent eradication of competing bacterial species may be contributing to the rapid spread of CA-MRSA. *Streptococcus pneumoniae* can produce hydrogen peroxide at concentrations capable of killing *S. aureus* [39], but this does not appear to be a major determinant of the patterns of co-colonization [42]. When looking specifically at CA-MRSA colonization, the rate of *S. aureus* colonization is increased in patients receiving the pneumococcal vaccine, but there is no particular increase in CA-MRSA strains [43]. Thus, streptococci on mucosal surfaces compete with *S. aureus*, but this is only one potential factor contributing to the current CA-MRSA outbreak.

Staphylococcus epidermidis resides more permanently on the skin because it is better able to tolerate the acidic pH, lipids, and salt found on skin [44] than is *S. aureus*, which can only persist on the skin for several hours. Recently, USA300, a CA-MRSA strain responsible for a rapidly spreading epidemic of skin and soft tissue infections, was found more frequently on the skin in the absence of nares colonization relative to other strains of *S. aureus* [34,35], suggesting that USA300 strains are particularly well adapted to persist on the skin. Whether skin colonization is permanent or transient, this colonization creates a major problem in hospitals because hands are an excellent means of transmitting MRSA, thus creating a major threat to patient welfare [45].

In addition to the two predominant staphylococcal human pathogens, several other staphylococci are capable of causing disease in humans and animals. *Staphylococcus saprophyticus* is able to colonize the urinary tract and cause infections, showing lower levels of colonization when higher concentrations of Tamm–Horsfall protein are present [46]. Coagulase-negative staphylococci are frequently found on the skin and mucous membranes [5], binding to tissues via teichoic acids, hemagglutinin, fibronectin, and autolysins [47,48]. *Staphylococcus anaerobius* is a pathogen of sheep that causes skin abscess, but only rarely has it produced abscesses or sepsis in humans [49].

Cell structure

The staphylococcal cell envelope is a complex structure that consists of a cell membrane composed of lipids and proteins, a cell wall made from peptidoglycan and teichoic acids, and polysaccharides. As with all cell membranes, its integrity is crucial for maintaining a boundary between the external environment and the cytoplasm. The membrane also contains a large number of proteins that transport solutes across chemical gradients, expending ATP or membrane potential. The electron transport machinery (NADH oxidase, cytochromes, and F_0F_1-ATPase) is also localized to the cell membrane, producing ATP and establishing the electrochemical gradient across the membrane that powers a multitude of activities. The cell wall contains the high osmotic pressure of the cytoplasm of staphylococci.

Membrane

The bacterial membrane is a lipid bilayer where the inner and outer leaflets contain asymmetrically placed lipids [50]. While the basic lipid components of the staphylococcal membrane were defined several decades ago [51] and found to change during different phases of growth [52], the ability of the membrane to respond to environmental, host defense-related, and antimicrobial challenges has only recently been appreciated.

The membrane phospholipids of *S. aureus* include phosphatidylglycerol, lysyl-phosphatidylglycerol, phosphatidic acid, cardiolipin, and traces of phosphatidylethanolamine and phosphatidylglucose [51–53]. These phospholipids,