**Staphylococcus aureus (subsp. aureus)**

**Host species**
- wide range of domestic and wild mammalian animals, birds, humans

**Properties**
- *S. aureus* exists in the environment such as dust, water, food or on food equipment and environmental surfaces, and it is relatively resistant to a variety of environmental conditions such as drying, UV light, and heat (National Research Council 1991, Shimizu 1994, Harkness & Wagner 1995). This environmental resistance and the broad host spectrum make it difficult to control spread of infection.
- *S. aureus* easily develops antibiotic resistance (Shimizu 1994, Winn et al. 2006). This is particularly a problem in *S. aureus* strains derived from hospitalized humans. They are typically resistant to multiple antibiotics including methicillin and oxacillin. The prevalence of such strains is lower in the community and in animal facilities, because antibiotic selective pressure is much lower than in hospitals.

**Organotropism**
- common inhabitant of the skin and mucous membranes (nasopharynx, lower intestinal tract, lower genital tract)
- entry into the body occurs most probably through breaks in the oral mucosa or skin

**Clinical disease**
- clinical signs (other than sudden death from pneumonia, septicaemia, or toxaemia) in laboratory animals include fever, anorexia, depression, various forms of dermatitis, foot swelling, reddening of the conjunctiva, lacrimation, subcutaneous lumps, enlarged mammary glands, and purulent discharge
• skin lesions are frequently accompanied by pruritus resulting in scratching and self-mutilation

Pathology
A variety of distinct disease processes have been reported in laboratory animals (National Research Council 1991, Shimizu 1994, Harkness & Wagner 1995, Percy & Barthold 2007), including the following:

• mouse: suppurative or ulcerative dermatitis, furunculosis, conjunctivitis, facial abscesses, botryomycotic granulomas, subcutaneous abscesses, preputial gland abscesses, bulbourethral gland abscesses, balanoposthitis, urinary cystitis
• rat: ulcerative dermatitis, pododermatitis, keratoconjunctivitis, panophthalmitis, subcutaneous abscesses
• guinea pig: exfoliative dermatitis, pododermatitis ("bumblefoot"), conjunctivitis, pneumonia, mastitis, osteoarthritis
• rabbit: conjunctivitis, subcutaneous abscesses, bronchopneumonia, lymphadenitis, mastitis
• hamster: dermal abscesses
• Mongolian gerbil: dermatitis ("sore nose").

In humans, a variety of suppurative inflammatory conditions and toxinoses are found (Winn et al. 2006):

• suppurative inflammation: skin lesions (e.g. furunculosis, impetigo), pneumonia, mastitis, phlebitis, meningitis, osteomyelitis, endocarditis, etc.
• toxinoses: toxic epidermal necrolysis, toxic shock syndrome, food poisoning.

Morbidity and mortality
Morbidity and mortality are highly variable and influenced by host, bacterial, and environmental factors:

• strain differences in susceptibility to S. aureus infection and associated disease are found among immunocompetent mice (Shults et al. 1973, Needham & Cooper 1976, Hong & Ediger 1978, von Köckritz-Blickwede et al. 2008); e.g. in the latter study, C57BL/6 mice were the most resistant in terms of control of bacterial growth and survival, A/J, DBA/2, and BALB/c mice were highly susceptible, and C3H/HeN, CBA, and C57BL/10 mice exhibited intermediate susceptibility levels
• immunodeficient hosts such as splenectomized or neutrophil-depleted mice (Teixeira et al. 2008, Robertson et al. 2008), athymic nude mice (Sano et al. 1988), iNOS-deficient mice (McInnes et al. 1998), TLR2-deficient and MyD88-deficient mice (Takeuchi et al. 2000) are highly susceptible to S. aureus infection or associated disease; likewise, certain mutant strains of mice without (known) immunodeficiency such as mice deficient in urokinase-type plasminogen activator have an increased susceptibility to staphylococcal disease (Shapiro et al. 1997)

• the genetic background strain may influence outcome of disease in mutant mice such as S. aureus-triggered sepsis and arthritis in IL-4-deficient mice (Hultgren et al. 1999)

• female and castrated CD-1 mice are more susceptible to infection with certain strains of S. aureus, suggesting a hormonal influence on resistance (Yanke et al. 2000)

• other contributing host factors are age (Girgis et al. 2004), physical injuries, e.g. as a result of fighting or surgery, and behavioural dysfunctions such as trichotillomania (Jacoby et al. 2002, Percy & Barthold 2007)

• S. aureus strains can express a diverse arsenal of virulence factors and differ in virulence (Mizobuchi et al. 1994, Benton et al. 2004, Sibbald et al. 2006)

• predisposing environmental factors include stress, e.g. provoked by experimental procedures, nutritional deficiencies (Galler et al. 1979, Chew et al. 1985, Wiedermann et al. 1996), concurrent infections, e.g. with mites (Percy & Barthold 2007) or Pseudomonas aeruginosa (Hendricks et al. 2001), and the prevalence of S. aureus in the environment

Zoonotic relevance

• transmissible between species

• transmission mainly by contact with infected animals or humans and their excretions

• humans are a reservoir: ~20% of people persistently carry S. aureus in the anterior nares, and ~60% are intermittent carriers (Kluytmans et al. 1997)

Interference with research

S. aureus could principally interfere with research by induction of disease (as described above). In addition, natural infection with S. aureus could compromise numerous studies using experimental animal models of S. aureus infection (e.g. models of implant-related infection, surgical wound infection, infected burn wounds, septic shock, infective endocarditis, and bone infection). It also has to be considered that S. aureus produces a
variety of biologically active products, including protein A, catalase, coagulase, fibrinolysins, hyaluronidase, lipases, hemolysins, leucocidin, exfoliatins, enterotoxins, and toxic shock syndrome toxin (Winn et al. 2006). The effects of these products and their metabolites are numerous and are not covered by this monograph. The following list provides examples of potential research complications due to entire \textit{S. aureus} organisms:

\textit{Physiology}
\begin{itemize}
\item \textit{S. aureus} induces serum $\alpha_2$-macroglobulin in rats (Jinbo et al. 2001)
\item \textit{S. aureus} causes contractile dysfunction in the mouse heart (Knuefermann et al. 2004) and aorta (Cartwright et al. 2007)
\end{itemize}

\textit{Pathology}
\begin{itemize}
\item immunocompromised animals are at increased risk for pathological lesions caused by \textit{S. aureus}, e.g. kidney abscesses have been observed in infected rats following treatment with corticosteroids (Simmons & Simpson 1977)
\item inapparent wound infection with \textit{S. aureus} increases plasma fibrinogen levels, total leukocyte counts, and wound histology scores in rats (Bradfield et al. 1992)
\item \textit{S. aureus} and its peptidoglycan ameliorate glucocorticoid-induced impaired wound healing in rats (Chang et al. 1997)
\item \textit{S. aureus} and its peptidoglycan stimulate macrophage recruitment, angiogenesis, fibroplasia, and collagen accumulation in wounded rats (Kilcullen et al. 1998)
\item \textit{S. aureus} enhances inflammation, endothelial injury, and blood coagulation in mice with streptozotocin-induced diabetes (Tsao et al. 2006)
\item \textit{S. aureus} elicits marked alterations in the mouse airway proteome during early pneumonia, including an increase in antimicrobial peptides, opsonins, pro-inflammatory mediators, and coagulation proteins (Braff et al. 2007, Ventura et al. 2008)
\item spontaneous arthritis in MRL/lpr mice is aggravated by \textit{S. aureus} infection (Salinas-Carmona et al. 2009)
\end{itemize}

\textit{Cell biology}
\begin{itemize}
\item infection with \textit{S. aureus} induces a pro-inflammatory state in endothelial cells, as determined by expression of cytokines (Yao et al. 1995, Yao et al. 1996, Söderquist et al. 1998,
Strindhall et al. 2005), Fc receptors (Bengualid et al. 1990), and adhesion molecules (Strindhall et al. 2002)

- *S. aureus* enhances expression of Toll-like receptor 2 and MyD88 in microglia (Esen & Kielian 2006)
- *S. aureus* induces release of TNF-α and nitric oxide in murine macrophages (Paul-Clark et al. 2006)
- *S. aureus* enhances secretion of TNF-α, IL-1β and nitric oxide, and up-regulates expression of nitric oxide synthase and Toll-like receptor 2 in epididymal epithelial cells (Zhao et al. 2008)
- *S. aureus* induces expression of IL-6 and IL-12 (Bost et al. 1999), MHC class II molecules (Schrum et al. 2003a), CD40 (Schrum et al. 2003b), receptor activator of NF-κB ligand and prostaglandin E2 in osteoblasts (Somayaji et al. 2008)
- *S. aureus* induces apoptosis in osteoblasts (Tucker et al. 2000)
- *S. aureus* activates the early response genes c-fos and c-jun and activator protein-1, and induces proapoptosis genes Bad and Bak in pleural mesothelial cells (Mohammed et al. 2007)

**Immunology**

- *S. aureus* inhibits contact sensitivity to oxazolone by activating suppressor B cells in mice (Benedettini et al. 1984)
- *S. aureus* induces production of IFN-γ, TNF, and IL-6 in the bloodstreams, spleens, and kidneys of systemically infected mice (Nakane et al. 1995)
- systemic *S. aureus* infection induces a Th2 response (IL-4, IL-10) in the spleens of mice (Sasaki et al. 2000)

**Interactions with other infectious agents**

- low concentrations of *Pseudomonas aeruginosa* enhance the ability of *S. aureus* to cause infection in a rat model of orthopaedic wounds, while at the same time *S. aureus* lowers the rate of *Pseudomonas aeruginosa* infection (Hendricks et al. 2001)
- *S. aureus* serves as an iron source for *Pseudomonas aeruginosa* during in vivo coculture (Mashburn et al. 2005)
- *S. aureus* synergizes with Kilham rat virus infection to induce diabetes in BBDR rats (Zipris et al. 2005)
• co-infection of the cotton rat with *S. aureus* and influenza A virus results in synergistic
disease and increased induction of both pro- and anti-inflammatory cytokines (IL-1β, IL-6,
IL-10, IFN-γ) (Braun *et al.* 2007)

**Behaviour**

• rats with inapparent wound infection show decreased activity in open-field testing and
shorter duration of freezing behaviour (Bradfield *et al.* 1992)

**References**

sensitivity to oxazolone by activating suppressor B cells in mice. *International Archives of
Allergy and Applied Immunology* **73**, 269-73

aureus* infection of human endothelial cells potentiates Fc receptor expression. *Journal of
Immunology* **145**, 4278-83

Buyssse JM (2004) Large-scale identification of genes required for full virulence of

*Staphylococcus aureus* infection of mouse or human osteoblasts induces high levels of

Bradfield JF, Schachtman TR, McLaughlin RM, Steffen EK (1992) Behavioral and

cathelicidin antimicrobial peptides produced during early pneumonia to promote

Braun LE, Sutter DE, Eichelberger MC, Pletneva L, Kokai-Kun JF, Blanco JC, Prince GA,
Ottolini MG (2007) Co-infection of the cotton rat (*Sigmodon hispidus*) with *Staphylococcus*
*aureus* and influenza A virus results in synergistic disease. *Microbial Pathogenesis* **43**, 208-16


Hultgren O, Kopf M, Tarkowski A (1999) Outcome of *Staphylococcus aureus*-triggered sepsis and arthritis in IL-4-deficient mice depends on the genetic background of the host.
European Journal of Immunology 29, 2400-5


Mohammed KA, Nasreen N, Antony VB (2007) Bacterial induction of early response genes and activation of proapoptotic factors in pleural mesothelial cells. Lung 185, 355-65


Needham JR, Cooper JE (1976) Bulbourethral gland infections in mice associated with *Staphylococcus aureus*. *Laboratory Animals* 10, 311-5


Author: Michael Mähler

Date: 16/03/2009