Diploma Thesis

Impact of Routine Infectious Diseases Service Consultation on Applied Levels of Staphylococcus aureus Bacteremia Standards of Care and Outcomes of patients with *Staphylococcus aureus* Bacteremia

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Zusammenfassung:

Hintergrund: *Staphylococcus aureus* Bakteriämie (SAB) ist eine Erkrankung, die mit hoher Morbidität und Mortalität assoziiert ist. Strategien zur Verbesserung des Managements werden benötigt. Diese Arbeit untersucht den Einfluss einer routinemäßigen infektiologischen Konsiliartätigkeit auf die Adhärenz von *Staphylococcus aureus* Bakteriämie Management-Leitlinien und auf die Mortalität bei Patienten mit SAB.

Methodik: Krankendaten aller Patienten aus einer prospektiven SAB-Datenbank wurden aus dem EDV Krankendokumentationssystem (MEDocs) entnommen und anhand eines standardisierten Fragebogens untersucht. Alle Fälle von SAB an der Universitätsklinik für Innere Medizin Graz innerhalb von zweieinhalb Jahren vor und nach der Einführung einer routinemäßigen infektiologischen Intervention wurden in die Studie eingeschlossen. Die Analyse vor Einführung der Routine-Intervention erfolgte retrospektiv, danach wurden die Daten prospektiv evaluiert.

Resultate: Insgesamt wurden 138 Patienten mit *Staphylococcus aureus* Bakteriämie untersucht. Neun davon wurden aus der Überlebens- und Management-Analyse ausgeschlossen, da sie innerhalb von drei Tagen nach Abnahme der Blutkultur verstarben. Eine routinemäßige infektiologische Intervention erfolgte in 90 der 129 übrigen Fälle. Die Entfernung von intravaskulären Fremdkörpern (95% vs. 67%, $p<0.009$), die Abnahme von Folgeblutkulturen (88% vs. 26%, $p<0.001$), die Verwendung von parenteraler Staphylokokken-Betalaktamen bei MSSA (97% vs. 68%, $p<0.0001$), die adäquate Therapiedauer von mindestens 14 Tagen bei unkomplizierter Bakteriämie und mindestens 28 Tagen bei komplizierter Bakteriämie (88% vs. 30%, $p<0.001$) und die Durchführung einer Echocardiographie (87% vs. 18%, $p<0.0001$) wurden häufiger eingehalten, wenn eine infektiologische Intervention vor Ort erfolgte. Die Sterblichkeit der Patienten mit infektiologischer Intervention war signifikant niedriger als ohne Intervention ($p=0.028$).

Konklusion: Diese Arbeit zeigt, dass eine routinemäßige infektiologische Intervention das Management und die Adhärenz von Managementleitlinien in Patienten mit SAB verbessert. Die Mortalität bei Patienten mit SAB sinkt durch Einhaltung der Managementleitlinien. Eine routinemäßige infektiologische Intervention sollte für alle Patienten mit *S. aureus* Bakteriämie etabliert werden.

Abstract:

Background: *Staphylococcus aureus* bacteremia (SAB) is associated with high morbidity and mortality. Strategies to improve management and outcome of this disease are needed. This thesis determines the impact of routine infectious disease consultation (IDC) on adherence to standards of care and mortality due to SAB.

Patients and Methods: We analysed clinical records of all patients from a SAB database using a standardized questionnaire. The data collection was based on the hospital electronic data system MEDocs. All episodes of SAB from the department of internal medicine over two and a half years were used. Data from patients before establishment of routine infectious disease consultation were analysed retrospectively, data from patients with intervention were analysed prospectively.

Results: A total of 138 cases of *Staphylococcus aureus* bacteremia were evaluated. Nine patients were excluded because they died within three days after the blood culture was drawn. Infectious disease consultation was performed in 90 out of the remaining 129 cases. Removal of intravascular foreign bodies (95% vs. 67%, $p<0.009$), obtaining a follow-up blood culture (88% vs. 26%, $p<0.001$), use of a parenteral antistaphylococcal beta-lactam therapy for MSSA (97% vs. 68%, $p<0.0001$), adequate duration of treatment of at least 14 days for uncomplicated bacteremia and at least 28 days for complicated bacteremia (88% vs. 30%, $p<0.001$) and the performance of echocardiography (87% vs. 18%, $p<0.0001$) were adhered to more frequently with infectious disease consultation. Mortality decreased in patients who received infectious disease consultation ($p=0.028$).

Conclusion: This study showed that infectious disease consultation improves the management of SAB and the adherence to standards of care. Mortality from SAB decreases with infectious disease consultation. Routine infectious disease consultation should be established for all patients with *S. aureus* bacteremia.

Declaration in Lieu of an Oath

I hereby declare that the content of this thesis corresponds to my work, which has not been submitted for a degree at this University or any other institution, and that other sources of information used in the text have been clearly acknowledged.

Graz, the 13th of December 2011 Signature

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Eidesstattliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die vorliegende Arbeit selbstständig und ohne fremde Hilfe verfasst habe, andere als die angegebenen Quellen nicht verwendet habe und die den benutzten Quellen wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht habe.

Graz, am 13. Dezember 2011 Unterschrift

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And to God, who made all the things possible.

Content

List of Abbreviations

BC	Blood culture
BSI	Blood stream infection
°C	Degrees Celsius
CA	Community-Acquired
CDC	Centers for Disease Control and Prevention, USA
CMBCS	Continuous-monitoring blood culture systems
CO_2	Carbon dioxide
CoNS	*Coagulase negative staphylococci*
CPK	Creatine Phosphokinase
CT	Computed tomography
DNA	Deoxyribonucleic acid
E.g.	Exampli gratia
Eap	Extracellular adhesion protein
FISH	Fluorescence in situ hybridization
GPCC	Gram positive cocci in cluster
HA	Hospital-Acquired
HCA	Healthcare-Associated
HIV	Human Immunodeficiency Virus
ICU	Intensive Care Unit
IDC	Infectious Disease Consultation
IE	Infective endocarditis
IG	Immunoglobulin
IV	Intravenous
MHC	Major Histocompatibility Complex
MIC	Minimum inhibitory concentration
MRI	Magnetic resonance imaging

MRSA	Methicillin-Resistant *Staphylococcus aureus*
MSSA	Methicillin-Sensitive *Staphylococcus aureus*
NaCl	Sodium chloride
NNV	Negative predictive value
PBP	Penicillin binding protein
PBP2a	Penicillin binding protein 2a
PCR	Polymerase chain reaction
PNA	Peptide Nucleic Acid
PPV	Positive predictive value
S.	*Staphylococcus*
SAB	*Staphylococcus aureus* bacteremia
SPSS	Statistical Package for the Social Science
SSS	Scalded Skin Syndrome
TEE	Transesophageal echocardiography
TSS	Toxin shock syndrome
TSST	Toxin shock syndrome toxin
TTE	Transthoracic echocardiography
US	United States
USA	United States of America
VISA	Vancomycin Intermediate *Staphylococcus aureus*
VRSA	Vancomycin Resistant *Staphylococcus aureus*
Vs.	Versus
α	Alpha
ml	Millilitre(s)
µl	Microlitre(s)
%	Percent
$	Dollars

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1. Introduction

1.1 History

The recognition of *Staphylococcus aureus* dates back to the 19th century. The Scottish surgeon Alexander Ogston (1844-1929) first discovered this organism in 1880 as a bacterial cause of pus. Ogston was convinced of the importance of antisepsis advocated by Joseph Lister (1827-1912), so he moved away from the contemporary teaching that suppuration was an essential stage in wound healing, and commenced antiseptic techniques. Lister thought that air is the reason for putrefaction in surgical wounds.
Ogston elucidated the one of the major causes of acute putrefaction by opening a patient´s abscess and examining the stained smear of pus under the microscope. 1882 he named the structure seen during examination of the smear *staphylococci* from the Greek „*staphylè*“, meaning bunch of grapes. His hypothesis that the cause of an acute abscess was a special germ was proven. Another experiment to confirm the existence of staphylococci was the injection of pus from acute abscess into guinea pigs and mice, which caused new abscess formation accompanied by signs of septicemia. Furthermore, he took blood samples from the infected animals and also detected staphylococci. If the pus was dressed with carbolic acid or heat before the injection, no abscess was formed. Ogston also cultured staphylococci by incubating hens' eggs, which he vaccinated with pus. The content of the septic eggs had a similar pyogenic activity to that of original pus (1-3).

Anton J. Rosenbach (1842-1923), a German surgeon, discovered two different strains of staphylococci, *Staphylococcus aureus*, the Latin meaning for gold, and *Staphylococcus albus* (now called *epidermidis*), from the Latin word „albus“, which means white, because of the appearance of the colonies (4).

Sir Alexander Fleming (1881-1955), the famous Scottish biologist and pharmacologist, discovered Penicillin on September 28th 1928 by observing staphylococcal cultures that he had inoculated and then set aside. He recognised in his laboratory the antibacterial activity of a mold (*Penicillium notatum*) that contaminated the staphylococcal culture plate and named the substance Penicillin, which was published in 1929 in the British Journal of Experimental Pathology. In 1940 penicillin was developed as an effective therapeutic

substance and mortality rates due to *Staphylococcus aureus* dropped down (5,6). The most widely used natural penicillin is penicillin G (6,7). Sir Alexander Fleming won the Nobel Prize in Medicine 1945 together with Ernst Boris Chain and Sir Howard Walter Florey „for the discovery of penicillin and its curative effect in various infectious diseases“ (8).

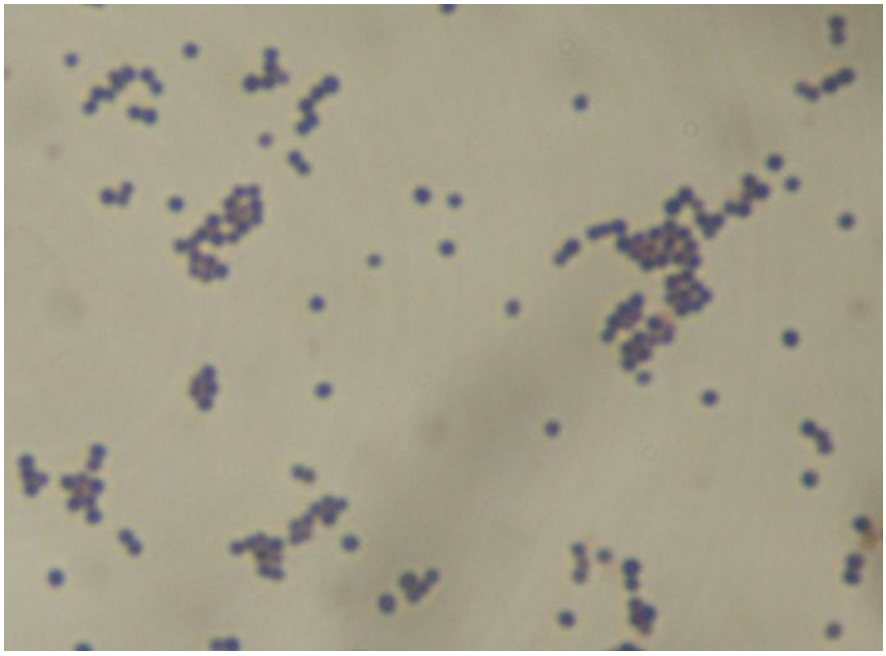
New challenges were Penicillin resistant strains of *S. aureus*, which were described almost immediately. After massive use of penicillin, 65-85% of staphylococci isolated from hospitals in 1948 were beta-lactamase producers and thus resistant to Penicillin G. In 1959, Methicillin, the world´s first semisynthetic type of staphylococcal beta-lactamase stable penicillin was introduced. The introduction of beta-lactamase resistant penicillin's (e.g., methicillin, nafcillin or oxacillin) provided a temporary respite, but infections due to nafcillin-resistant staphylococci emerged. In 1961 methicillin resistant *Staphylococcus aureus* cases in the United Kingdom were reported (7,9,10). Vancomycin, a glycopeptide antibiotic introduced in 1956, has been the major drug used for treatment of nafcillin-resistant *S. aureus* infections, but some strains developed intermediate susceptibility. Some *Staphylococcus aureus* strains with resistance to vancomycin have been described (11). After development of other antibacterial agents resistance to e.g. chloramphenicol, erythromycin, and tetracycline also emerged within the next decade (12).

1.2 Definition

1.2.1 Morphological, biochemical and metabolic characteristics

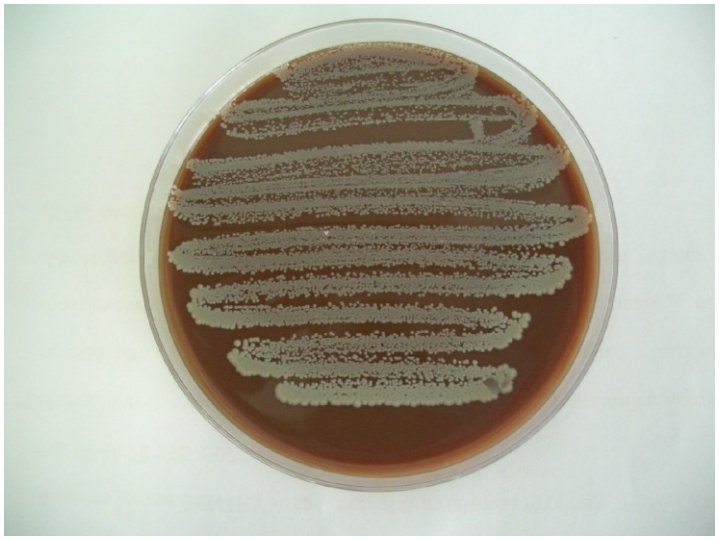
Staphylococcus aureus is one of the most common causative organisms of bloodstream infections. This name refers to the fact that the cells of these gram- positive cocci grow in a pattern resembling a cluster of grapes (Figure 1). The spherical cells are about 1 micron in diameter arranged in irregular clusters. Staphylococci are non-spore forming and non-motile (13).

Figure 1. Gram stain of *S. aureus*



This bacterium forms characteristic large gold-pigmented colonies that appear round, 1-2mm, golden yellow (Figure 2) in colour with a zone of complete haemolysis on blood agar. *S. aureus* is a facultative anaerobe that grows by fermentation which yields principally lactic acid. *S. aureus* can grow at a temperature range of 15 - 45° C and at NaCl concentrations as high as 15%, this ability has been utilized to develop selective media such as Mannitol Salt Agar. The optimum temperature is 30 - 37° C which correlates with the body temperature of the human host (14).

Figure 2. Characteristic gold/yellow colonies of *S. aureus*



Although more than 32 species and 15 serotypes of staphylococci have been described, just 16 of them colonise humans. The species of major medical importance are *S. aureus* (the most virulent and best-known member of genus), *S. epidermidis* and *S. saprophyticus*. *S. aureus* possesses the enzyme coagulase, which acts on plasma to form a clot. Other staphylococci (e.g. *S. epidermidis* and *S. Saprophyticus)* do not posses this enzyme and are termed as coagulase-negative staphylococci (Figure 3 and 4). In addition, *S. aureus* ferments mannitol and is sensitive to novobiocin and produces DNAase. Relatively simple biochemical tests can be used to differentiate *S. aureus* and the other *staphylococci* (15).

Figure 3. Positive coagulase test of *S. aureus* and negative coagulase test of *S. epidermidis*

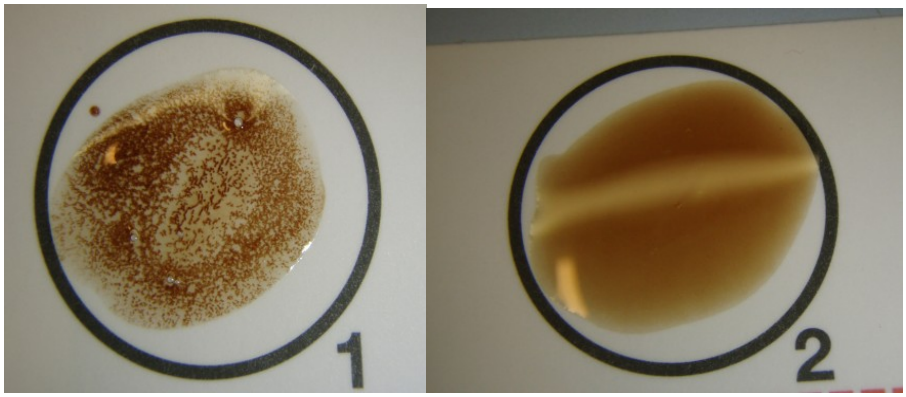
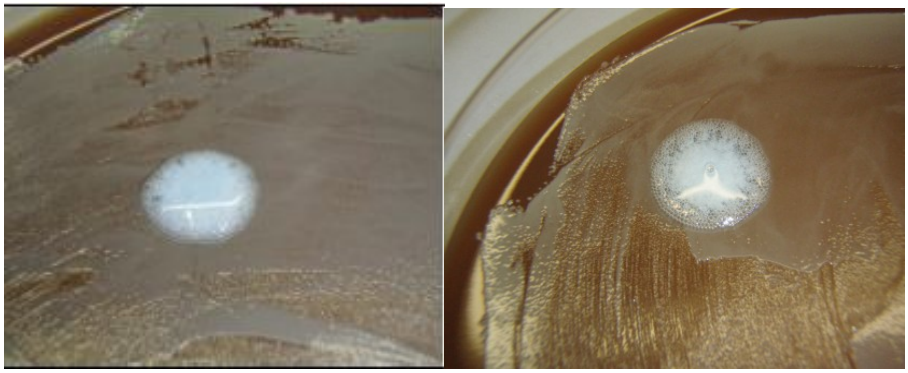


Figure 4. *S. aureus* and *S. epidermidis* positive catalase test



1.3 Epidemiology

1.3.1 Incidence, morbidity and mortality

Staphylococcus aureus is one of the leading causes of nosocomial and community-acquired bacteremias and associated with a high morbidity and mortality. It is the second most important bloodstream isolate after *Coagulase Negative Staphylococcus* and *E. coli*, responsible for 20% of hospital-acquired bacteremia, and is the most common source of bloodstream infection in persons 65 years of age and above (16,17). Most of the SAB data are available from the USA and Europe. Many of these countries have recorded a marked increase in incidence of *S. aureus* infections over the previous two decades. The noted increase in SAB incidence could be attributed to an increase in risk factors for *S. aureus* infection, due to a growing population at risk (18,19).

Lyytikäinen et al. analyzed data from 5,045 individuals with *Staphylococcus aureus* bloodstream infections in Finland from 1995 to 2001, they observed that the annual incidence for SAB increased by 55% from 11 per 100,000 population in 1995 to 17 in 2001. The rise in incidence of SAB in elderly person lead to an increase in annual mortality rate due to SAB from 2.6 to 4.2 deaths per 100,000 population per year (18). In Denmark, the SAB incidence rate increased from 1981 to 2004, on average 5.3% annually (20). Asgeirsson et al. demonstrated a retrospective study of 692 patients with a positive blood culture for *S. aureus* collected from 1995 to 2008 in Iceland. The incidence increased from 22.7 to 28.9 per 100,000 per year during that time ($p=0.012$). The 30-day mortality decreased from 25% to 8.1% ($p=0.001$) and 1-year mortality decreased from 37% to 27.9% (p 0.061) (19). In a population-based study conducted in Calgary (Canada) the average incidence rate of *S. aureus* bacteremia was estimated 19.7 cases/ 100,000 population with no significant change from 2000 to 2006. However, the MRSA rate increased dramatically during the same period ($p<0.001$) (16). A prospective multicenter study of SAB was performed on 505 patients in 6 US hospitals from 1994 to 1996 by Chang et al., they showed that the 30-day mortality among patients with endocarditis was 31% in compared to 21% who had SAB without endocarditis (21). In the University Hospital of Regensburg between 2004 and 2005 risk factors associated with long-term outcome in 119 patients with SAB were collected by Hanses et al. They found a 30-day mortality of 28.8%, the 90-day mortality was 37.5% and 1-year mortality was 47.5%. Their

results showed, that there was a better outcome in patients younger than 65 years compared to those older than 65 years, and a lower body mass index (BMI <24kg/m) was associated with a higher mortality (22). Before the antibiotic era, SAB had a mortality of approximately 80% (23). Actually, despite advances in antimicrobial therapy and intensive care support, the overall rate of mortality from staphylococcal bacteremia ranges from 11 to 43% (24,25).

1.3.2 Carriage

Because its primary habitat is moist squamous epithelium of the anterior nares, most invasive *S. aureus* infections are supposed to arise from nasal carriage. Three carriage patterns can be distinguished in the healthy adult population: persistent carriage, intermittent carriage and non-carriage (26). Approximately 20–30% of persons are colonized persistently with *S. aureus*, 30% are colonized intermittently, and 50% are never colonized. Rates of staphylococcal colonization are high in patients with diabetes type 1, patients undergoing haemodialysis, surgical patients, intravenous drug users, and patients with the acquired immunodeficiency syndrome. These individuals are also at enhanced risk for staphylococcal disease (27). Notably, persistent carriers have higher bacterial loads than intermittent carriers and a higher risk of developing invasive infection. In a large study conducted by Eiff et al. >80% of isolates from bacteremic *S. aureus* infections were identical to strains carried by these individuals (28). A carrier may be unaware of the potential pathogenicity of the bacteria that they harbour, both for themselves and others. Infections are caused by the colonizing strain after entrance to a normally sterile site due to trauma or excoriation of the skin or mucosal surface. Carriers of *S. aureus* who undergo medical procedures are at risk of developing bacteremia (29). Many of these infections can rapidly be life-threatening if not treated and managed appropriately.

1.3.3 Transmission

S. aureus dissemination occurs by direct transmission from human to human via skin contact, via environmental contamination of fomites or through air, by contact to animals

or to contaminated material. Most community acquired *S. aureus* infections are auto-infections with strains carried in the anterior nares, on the skin and perineal area. Depending on the carrier status the *Staphylococcal aureus* strains persist for weeks/months or remain, and can survive on dried materials for months. Relapsing skin infections can therefore also result from use of clothing contaminated with *S. aureus* from a previous infection (30). Patients colonized with *S. aureus*, health care professionals and septic lesions due to *S. aureus* are the major sources for nosocomial *S. aureus* infections. Health care workers either colonized or not, can transmit *S. aureus* via hand contact in the case of inappropriate hand hygiene measures. The organism can then be disseminated to various body sites and, if there is skin injury (e.g. vascular catheterization or surgical incision) an infection can occur.

1.4 Pathophysiology and virulence factors

The human immune system has developed complicated mechanisms to prevent infection, but *S. aureus* like other bacteria, produces an incredible variety of virulence factors, including a minimum of five cytolytic or membrane damaging toxins (alpha, beta, gamma, delta and leukocidin), as well as exofoliative toxin, toxic shock syndrome toxin (TSST-1) and five enterotoxins (A to E) that assist the bacteria to colonize the host, cause infection and diseases, and especially prevent the immune system from responding to the bacteria. None of these factors alone is considered to be the primary virulence mechanism of *S. aureus* infection, the combination of multiple factors is responsible for *S. aureus* pathogenicity (15,29).

Adhesion and Colonization: *S. aureus* has the competence to up-regulate virulence factors that allow the bacteria to effectively adhere to and colonize the host cells. Essential for this process is the Teichoic acid, a polymer on the surface of *S. aureus* (31,32).

Invasion: The term is commonly used to describe the entry of bacteria into the host organism. *S. aureus* produces proteins like exfoliative toxins, haemolysins (alpha-toxin) and different enzymes that help in the invasion of host tissue by destroying it. This often as a consequence in addition to the immune cells also kills erythrocytes, which could attribute

to anaemia. The virulence factors are much more effective in person with weakened immune system (e.g. infants or HIV patients) or damage in the physical integument and going on inflammatory processes (15,27).

Evasion: After crossing the mucosal or skin barrier, *S. aureus* evades the host immune response by secreting anti-opsonising proteins (e.g. chemotaxis inhibitory proteins) to avoid phagocytosis by neutrophils. Protein A, located on the surface of *S. aureus* cells, also has antiphagocytic characteristics (33). Furthermore, *S. aureus* secretes leukotoxins (e.g., Panton-Valentine-leukocidin) that lyse leukocytes (27), and expresses superantigens (e.g. TSST and staphylococcal enterotoxins) (34), which subvert the humoral immune response.

Biofilms: The biofilm is a layer that helps the *S. aureus* to survive under crude conditions and in a metabolically inactive state, is a structured community of microorganism imbedded in a self-generated polymer matrix called glycocalyx and attached to an inert, non-living surface or living tissue. Biofilm formation starts with the adherence of the bacteria to the surface, influenced by many attractive or repulsive forces arose between bacteria and surface. The next important step is multiplication and surface accumulation of the bacteria. Many genes are involved in biofilm formation, regulation of metabolic pathways and the production of virulence factors. The exopolysaccharide matrix protects the bacteria from the host immune reaction and is a diffusion barrier for some antibiotics. Infections associated with biofilms, such as infections of central venous catheters, native and prosthetic valve endocarditis, urinary tract infections, septic arthritis and cystic fibrosis are difficult to treat because of the fact, that bacteria within the biofilm tend to develop marked resistance to antibiotics in contrast to the same strain of bacteria broth in that grow free-living (35).

1.5 Diseases caused by *Stapyhlococcus aureus*

S. aureus is a human pathogen responsible for various infectious diseases. Most of *S. aureus* infections are localized to the skin and are not severe, but sometimes they progress to systemic infections and can become life-threatening (13).

Pyogenic infection

Skin infections include pyoderma (e.g. follicullitis, furuncles, carbuncle, and impetigo) and soft tissue infections (e.g. cellulitis, erysipelas, and pyomyositis). Blood stream infections, infective endocarditis, meningitis, pericarditis, pulmonary infections, osteomyelitis, septic arthritis, septic bursitis and pyomyositis.

Toxin-mediated disease

Staphylococcal Scalded Skin syndrome (SSSS), Staphylococcal Toxic Shock Syndrome (STSS) and Staphylococcal food poisoning.

The following chapter is limited to the introduction of some life-threatening *S. aureus* infections.

1.6 *Staphylococcus aureus* bacteremia

1.6.1 Definition

Bacteremia, also termed septicaemia, is a blood stream infection and one of the most common complications of *S. aureus* infection (36). Bacteremia is defined as the presence of viable bacteria in the blood and is not necessarily associated with clinical manifestation of diseases. The diagnosis of blood stream infection (BSI) needs the isolation of one or more pathogens from at least one blood culture and the presence of clinical signs or symptoms of systemic infection within 24 hours of a positive blood culture being collected (37). Septicemia is defined as invasion of the bloodstream by virulent microorganisms (as bacteria, viruses, or fungi) from a focus of infection that is accompanied by acute systemic illness, called also *blood poisoning* (38).

In nosocomial SAB the infection results from using intravascular lines, while in community acquired SAB the infection results from skin- and soft tissue infections (39). Differentiation between uncomplicated and complicated SAB is necessary to optimize antibiotic therapy.

1.6.2 Uncomplicated SAB

There are different definitions regarding uncomplicated SAB. Fowler et al. conducted a study between 1994 to 1996 in 244 patients, to determine, if the recommendations of infectious disease specialists affect the clinical outcome for hospitalized patients with SAB. Before the study started they defined uncomplicated SAB by the occurrence of all these criteria (40):

1. TEE negative for vegetations and predisposing valvular abnormalities on day 5-7 of therapy
2. Negative surveillance blood cultures 2-4 days after initiation of appropriate antibiotic therapy and removal of focus
3. Removable focus of infection
4. Clinical resolution (afebrile and no localizing complaints attributed to metastatic staphylococcal infection)
5. No indwelling prosthetic devices

Uncomplicated bacteremia has been defined by Jenkins et al. as a case that fulfils following criteria (41):

1. A negative blood culture 2-4 days after starting treatment
2. And the absence of infective endocarditis, metastatic infection and other deep- tissue infection.

Naber et al. summarized the outcome of the Clinical Consensus Conference on Gram-positive Bloodstream Infections held in 2007, concerning the definition of uncomplicated SAB, no consensus could be reached. However they defined criteria for uncomplicated SAB as following (42):

1. Catheter-associated infection
2. Negative follow- up blood culture
3. Defervescence within 72h of starting therapy
4. Normal TEE
5. No prosthetic material (joints or cardiovascular system)
6. No clinical signs suggestive of metastatic infections

1.6.3 Complicated SAB

Complicated bacteremia is present in patients with an established deep source of infection, or persistent bacteremia.

Fowler et al. defined complicated SAB by occurrence of one or more of the following criteria (40):

1. Predisposing valvular abnormalities (more than mild regurgitation) but no vegetations shown by TEE
2. Positive surveillance blood culture
3. Superficial, non-removable focus of infection
4. Persistent signs of infection after 72h of antibiotic therapy

From January 2004 to December 2005 Fowler et al. conducted a study on 724 patients admitted to Duke University Medical Centre, North Carolina with SAB. All patients were followed for 12 weeks after the initial positive blood culture for the progress of the primary outcome that was "complicated bacteremia". "Complicated bacteremia" was defined as the presence of either (a) mortality attributed to SAB, (b) complicated infection present at the time of the initial hospitalization, (c) embolic stroke, or (d) recurrent infection within the 12-week follow up period. "Complicated infection at the time of initial hospitalization", was defined as the presence of a site of infection remote from the primary focus caused by either (I) haematogenous seeding including (but not limited to), infectious endocarditis, septic arthritis, deep tissue abscesses, vertebral or sacral osteomyelitis, epidural abscesses or (II) extension of infection beyond the primary focus including septic thrombophlebitis of abscess (43). In a previous study Jenkins et al. used the following definition of complicated bacteremia: “A sample for follow-up blood culture obtained 2-4 days after the initial culture grew *S. aureus*, the presence of spread of infection, infection involving a prosthesis not removed within 4 days, or evidence of infective endocarditis” (41).

1.6.4 Definition of blood stream infections according to the mode of acquisition

There is still no consensus on the definition of the terms used to describe the mode of acquisition. Some authors consider SAB to be hospital acquired if the first positive blood culture was drawn after 48 hours of hospitalisation and community acquired SAB was defined a positive *S. aureus* blood culture obtained within the first 48 hours of hospitalization from a patient (18,44,45). Fowler et al. defines the terms in one his papers (40) as follows: Hospital acquired SAB is if a positive blood culture was drawn after more than 72 hours of hospitalization, community acquired if it was obtained within 72 hours of admission from a patient without extensive health care contact. Like many other authors and scientists Fowler et al. feel the need to define a new third category, namely "health care associated SAB", because of the increasing number of patients that are in touch with health care institutions and their SAB is rather related to this factor than to community acquired bacteremia. They defined health care associated SAB as a positive blood culture draw within 72 hours of hospitalization from a patient with intensive contact to health care systems (haemodialysis, surgery, presence of an indwelling intravascular catheter) (40). The characteristics of HCA-BSI are not concurrently defined among studies, but most authors appoint previous hospitalization, residence in nursing home or long-term care facility, history of haemodialysis or surgery and outpatient iv. therapy at home as the most important features (46-48). Shorr et al. analyzed a large US-database to identify patients with BSI from 2002 to 2003 and showed, that the rate of *S. aureus* causing HCA-SAB was 25.7%, HA-SAB 29.7% and CA-SAB was 17.8%, the rest (26,8%) was distributed to other pathogens (e.g. gram negative bacteria, fungi). Patients with HA-SAB received an earlier diagnosis and treatment than patients with CA-SAB (49).

1.7 Risk factors

Humans and animals have abundant normal skin flora that usually does not cause disease, but through a breakdown of the body´s defences bacterial infection can occur. However, the skin is subject to repeated minor traumas that are often unnoticed which destroy its integrity and allow organisms to gain access into underlying tissue and cause an

inflammatory response. In most instances, this inflammation is limited to the skin, but bacteria can spread to deeper tissue or enter the bloodstream.

Older age, the type and site of infection and underlying comorbidities are risk factors associated with a risk of death from bacteremia (45,50). Community-acquired SAB is related to host factors and carrier status and seen in younger patients with less comorbidities. Hospital acquired SAB is more frequently seen in older patients with underlying diseases.
Several factors associated with an increased risk of developing healthcare associated or nosocomial SAB have been identified, including previous *S. aureus* infection or colonization, diabetes mellitus, skin ulcers or cellulitis at hospital admission, infections in patients receiving haemodialysis, patients with rheumatoid arthritis and cardiovascular disease, injection drug use, liver disease and alcohol abuse. Patients with implanted medical devices, such as inserted venous catheters, artificial heart valves or prosthetic joints are also at high risk for developing SAB (20,51-53).

As already mentioned nasal carriage of *S. aureus* is a major risk factor especially for patients with immunosuppressive conditions, use of corticosteroids or human immunodeficiency syndrome (HIV), wound infections and patients in intensive care units.
MRSA bacteremia is more frequently found in healthcare institutions, and the risk factors include medical procedures, longer hospital stay and prior antibiotic exposure.
Coello et al. prospectively followed a cohort of 479 hospital patients, initially only colonized with MRSA, for the development of MRSA infection and found that 11.1% developed nosocomial MRSA infection. Pujol et al. conducted a prospective cohort study on 488 patients and found that around 22% of the patients colonized with *S. aureus* at that time were subsequently admitted to intensive care unit (ICU) because of bacteremia (54,55).

1.8 Complications

SAB carriers are at increased risk for bacteremia and thus for complications like metastatic infection, endocarditis, severe sepsis and recurrence. About one-third of patients with SAB

generate distant septic metastases or local complications. The frequency of such complications from SAB ranges from 2 to 47%. The most common sites of septic metastases in a study conducted by Ringberg et al. were the bones, heart valves, lungs and joints (43,56). Fowler et al. performed a prospective study from September 1994 through December 1999 on 724 patients, 43% of them had complicated SAB. They identified four risk factors related to complicated SAB: the presence of persistent bacteremia (positive follow- up blood culture result drawn 72-96 hours after initiation of adequate treatment), community acquisition, fever persisting for more than 72 hours and the presence of skin lesions suggestive of metastatic infection. If none of the identified factors was present, the likelihood to develop a complication was 16%. In this study endocarditis was the most common complicated infection (39%) (43).

1.8.1 Endocarditis

Endocarditis is an infection of the endocardial surface of the heart. Most infections occur on heart valves, but also can arise on shunts, septal defects or on the mural endocardium (15). *S. aureus* is the most common cause of bacterial endocarditis in structurally normal cardiac valves (57). The clinical outcome is essentially related to the virulence of the infecting bacteria. Transient bacteremia is common and usually not clinically important, but if the organism is of high virulence, it can colonize, proliferate and damage the heart. Bacteria can adhere and form vegetations. *S. aureus* endocarditis mainly occurs in elderly patients, intravenous drug users, patient´s with prosthetic valves and hospitalized patients (27). Chang et al. confirmed in their study, that the risk factors for endocarditis are community acquisition of bacteremia, history of endocarditis, i.v. drug abuse, valvular heart disease and unknown source of infection (21). In a study conducted by Fowler et al. on 724 patients that had at least one blood culture positive to *S. aureus*, 12% had endocarditis (43). Intravenous drug users are mainly younger patients with right-sided endocarditis. They also show lower mortality rates. Left-sided endocarditis is more frequently seen in elderly patients, is usually not associated with intravenous drug use, they show a high mortality rate and an involvement of the heart valves (27). In a prospective observational cohort study which enrolled 1779 patients in 39 centers in 16 countries from 2000 to 2003, the most common cause of all IE (31.6%) was *S. aureus* (27.4% MRSA)

followed by viridans group streptococci (18%). In this study patient with *S. aureus* IE more often were female, dependent on haemodialysis, had diabetes mellitus and were more likely to have healthcare associated IE (39.1%) than patients with IE caused by other bacteria (58).

IE due to MSSA is not anymore just a community-acquired problem due, because of the increased frequency of invasive procedures, use of prosthetic devices (long term intravascular catheters, orthopaedic, cardiovascular and other devices), and an increasing number of immunodeficient patients. Chang et al. performed a study in 6 university hospitals on 505 patients and gained similar results to Fowler et al., the rate of endocarditis defined by modified Duke Criteria (see Table 2) was 13%. In the study they also compared MRSA versus MSSA endocarditis and reported that 69% of the cases (out of the 13% who had endocarditis) were due to MSSA and 31% due to MRSA. Epidemiologically, MSSA IE occurs more frequently in intravenous drug users, persons with previous endocarditis and is more often community acquired. MRSA IE is more likely to be hospital acquired, more common in elderly patients and associated with persistent bacteremia (21).

IE can be difficult to diagnose, because the clinical manifestations may be restricted. In a study conducted by Fowler et al. with the goal to examine the role of echocardiography in patients with SAB, only 7 (7%) of 103 patients showed clinical signs of IE, like a new murmur or autoimmune phenomena. Only 5 out of 7 patients fulfilled the modified Duke Criteria for IE (59). Echocardiography is a useful diagnostic measure for the diagnosis of endocarditis. There are two modalities that are used today for diagnosis of IE: Transthoracic echocardiography (TTE) and Transesophageal echocardiography (TEE) (60). The impact of these methods have been elaborated further later in this paper. Table 1 and 2 show the Duke Criteria used to establish a diagnosis of endocarditis.

Table 1. Definition of terms used in Duke Criteria for diagnosis of IE (61)

Major Criteria

1. Positive blood culture for IE

A. Typical microorganism for infective endocarditis from two separate blood cultures:

(i) viridans streptococci, *Streptococcus bovis*, HACEK group, *Staphylococcus aureus*; or

(ii) community-acquired enterococci in the absence of a primary focus, or

B. Persistently positive blood culture, defined as recovery of a microorganism consistent with infective endocarditis from:

(i) at least 2 positive blood cultures drawn >12 h apart; or

(ii) all of 3 or a majority ≥ 4 separate blood cultures (with first and last drawn at least 1 h apart)

(iii) single positive blood culture for *Coxiella burnetii* or phase I IgG antibody titer of >1:800

2. Evidence of endocardial involvement

A. Positive echocardiogram for IE defined as :

(i) oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, in implanted material, in the absence of an alternative anatomic explanation, or

(ii) abscess, or

(iii) new partial dehiscence of prosthetic valve, *or*

B. New valvular regurgitation (worsening or changing of pre-exsisting murmur not sufficient)

Table 1, *continued*

Minor Criteria

1. Predisposition: predisposing heart condition or injection drug use
2. Fever: temperature ≥38.0°C
3. Vascular phenomena: major arterial emboli in form of Janeway lesions and petechiae (Figure 5), septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages,
4. Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor
5. Microbiologic evidence: positive blood culture but not meeting major criterion as noted previously[a] or serologic evidence of active infection with organism consistent with infective endocarditis

[a]Excludes single positive cultures for *coagulase-negative stahylococci* and organisms that do not cause endocarditis

Figure 5. Embolic skin lesion due to *S. aureus*

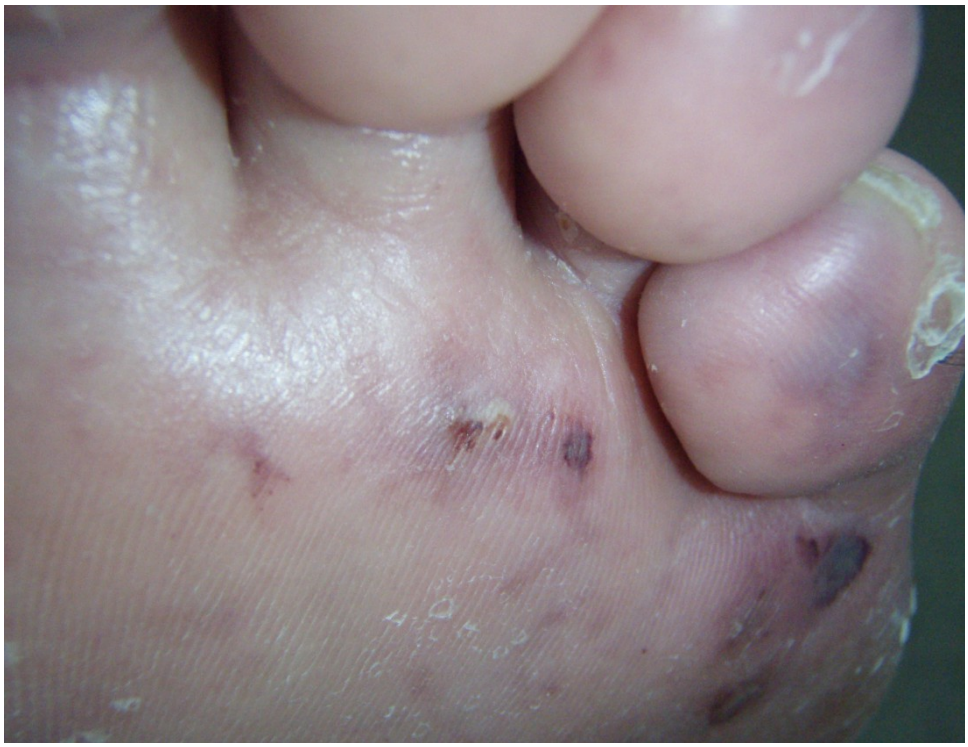


Table 2. Duke criteria for clinical diagnosis of infective endocarditis, with modification (61)

1.Definite infective endocarditis

A. Pathologic criteria

(i) Microorganisms demonstrated by culture or histologic examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or

(ii) pathologic lesions; vegetation or intracardiac abscess confirmed by histologic examination showing active endocarditis

B. Clinical criteria[a]

(i) 2 major criteria; or

(ii) 1 major criterion and 3 minor criteria; or

(iii) 5 minor criteria

2. Possible infective endocarditis

(i) 1 major criterion and 1 minor criterion; or

(ii) 3 minor criteria

3. Rejected

(i) firm alternate diagnosis explaining evidence of infective endocarditis; or

(ii) resolution of infective endocarditis syndrome with antibiotic therapy for ≤4 days; or

(iii) no pathologic evidence of infective endocarditis at surgery or autopsy, with antibiotic therapy for ≤4 days; or

(iii) does not meet criteria for possible infective endocarditis, as above

[a] See Table 1 for major and minor criteria definiton

1.8.2 Other complications

Metastatic complications are the second most common complication after IE. The most common sites of metastatic foci are bones and joints, epidural space and intervertebral discs and visceral abscesses in different organs like lungs, spleen, liver and kidney. Jenkins et al. defined metastatic infection as a “microbiological or radiographic evidence of *S.*

aureus infection caused by haematogenous seeding“ (41). In the study of Fowler et al. 228 patients out of 724 had complicated infections, the most frequent were septic arthritis (24%), deep tissue abscess (18%) and vertebral osteomyelitis (10%) (43). Ringberg et al. also found septic metastasis in 36 out of 68 patients (53%), 18 patients had bone metastasis (56). Metastatic complications are associated with a longer need for antibiotic treatment and for surgical procedures. Suppurative accumulations at any sites and inadequate treatment can lead to recurrent infection, which is a major complication (43). A recurrence can be due to reinfection (infection with another strain) or relapse (infection with the original strain) (62). The reported rates of recurrence in *S. aureus* infections range from 5 to 12% (11,27,62). Kreisl et al. conducted a study to estimate the rate of recurrence of SAB and its association with adequate antibiotic therapy from 1995 to 2004 on 397 patients. The rate of recurrence was 17%. Risk factors supporting recurrence were HIV infections, diabetes and infection due to MRSA. They did not find an association of inadequate antibiotic therapy and a higher risk for recurrence (63). In contrast to Kreisl et al., other authors' data expose an association between inappropriate antibiotic therapy and an increased risk for recurrence (64,65).

1.9 Economic impact

SAB represents a notable burden on health care systems. It is related to higher treatment costs and longer duration of hospital stay in average than bacteremia caused by any other pathogens (66).

Noskin et al. conducted a study on ~1000 US hospitals, to determine the connection between SAB and length of hospital stay, total charges and in hospital mortality. They found, that inpatients with *S. aureus* infections had 3 times longer mean length of hospital stay (14.3 vs. 4.5 days; $p<0.001$) than other inpatients. As a result the treatment costs increased 3-fold (67). Rubin et al. performed a study in 1995, on 13,550 patients with SAB in New York City, showed that the length of hospitalization (20 vs. 9), the hospital charges ($ 32.100 vs. $ 13.263) and the mortality (10% vs. 4%) for inpatients with SAB were twice as high as for patients without SAB (68). In another study that involved 348 patients with SAB, both the length of stay in hospital (7 vs. 9 days) and hospital costs ($ 19.212 vs. $ 26.424) of patients with MRSA were significantly higher than in patients with MSSA

bacteremia (69). Similar results were reported by Abramson et al., they showed, that patients with MRSA compared to patients with MSSA regarding length of stay (12 vs. 4 days) and total charges ($ 27.083 vs. $ 9.661), the burden of disease was increased (70).
However, the exact economic cost of SAB is not really applicable to other locations, because the scope of each of the authors is limited by many factors, like the area where the study is conducted, the cohort of patients, the physician fees, hospital. Complications associated with SAB, inappropriate antibiotic therapy, resistance to antimicrobial drugs are important health but also economic problems (71,72).

1.10 Control measures

Many different measures have been recommended for controlling health care associated *S. aureus* blood stream infections. Despite the numerous literature on the topic, the outcome of intensive control measures on the patients with SAB as well as the most successful surveillance strategy remain considerably controversial. Based on single studies it is evident that 20-30% of nosocomial infections could be avoided by organized infection control programs (73). Guidelines that are more commonly recommended for preventing the spread of MRSA among hospitals and communities suggest the following measures: education of healthcare workers, with realization and adherence to hand-washing practices, limitation of antibiotic use, active surveillance cultures, contact isolation of MRSA-positive patients and prophylactic isolation of high-risk patients (74,75).

Hand washing is considered as one of the most important measures for preventing the spread of infectious agents. Already in 1847, Semmelweis realized that an antiseptic hand wash could reduce the incidence of puerperal fever (76). Health care workers should decontaminate their hands with antiseptic containing preparation before and after all patient contacts.

Medical surveillance has a preventive emphasis. It´s primary goal is to detect (and - if possible - eliminate) new or uncontrolled risks in hospitals and health care institutions.
The starting point for controlling the factors influencing the spread of epidemiologically significant pathogens, are surveillance data of nosocomial infections. Active surveillance

cultures are necessary to identify the pool of spread (77). Nasal decolonization has been shown to be effective in many patients, and is recommended in *S. aureus* nasal carriers who are admitted to the hospital or who are provided to undergo medical procedures shortly (78). Combined topical treatments for five days with mupirocin and clorhexidine for decolonization of the nose and the skin achieved a success rate of 87% (79,80).
However, in a study conducted by Jones et al., topical mupirocin showed a resistance in 13% of MRSA strains and a high level resistance in 9%, despite the moderate use of mupirocin in the hospital (81).

1.11 Laboratory diagnosis

1.11.1 Blood cultures

A blood culture is defined as a specimen of blood obtained from a single venipuncture or intravenous access devise that is cultured in specialblood culture media and observed for growth in automatic blood culture detection systems. This diagnostic measure provides beneficial information for the management and the determination of effective antimicrobial therapy for the individual patient (82). Blood samples for blood culture should be collected on suspicion of presence of bacteria or fungi in the blood and before antimicrobial treatment is started, especially in the presence of a positive predictor for bacteremia such as increased temperature >37.8° C, leukocyte count >12000 cells/µl, tachycardia (heart rate of >90beats/min), age over 30 years, the presence of a central venous catheter and a hospitalization for more than 10 days (83). Previous studies showed, that two to three blood cultures obtained within 24h could detect 99% of bloodstream infection (84,85).
Newer studies found that the obtained volume for blood cultures is essential to detect BSI more frequently (86-88). Cockerill et al. also studied the volume of blood culture to yield of microorganism relationship and showed that the recovery of pathogens increases with an increase volume of blood culture obtained (yields form 20mL and 30mL blood were 29.8% and 47.2% greater than those from 10mL blood culture). The optimal number of serial cultures needed to detect bacteremia is three pairs of peripheral blood cultures (three aerob and three anaerob), each of them with a yield of 5-10 mL (86,89,90). The first conclusion that can be drawn is, the greater the volume of blood cultured, the better the yield of

microorganisms (82). However, culture of more than 60ml blood seems to be of no benefit (86,90). The second conclusion is that it is not significant for the detection rate, if the multiple blood cultures are obtained contemporary or in intervals within 24 hours period (86). There is a wide spectrum of blood culture systems ranging from simplest manual detection systems, fully automated detection systems to continuous-monitoring blood culture systems (e.g. BACTEC® or BacT/Alert®).

1.11.2 Rapid tests

1.11.2.1 Gram stain

Gram staining is the first line diagnostic procedure from positive blood culture bottles. Gram positive, Gram negative and fungal pathogens can thus be identified, but further differentiation is not possible.

1.11.2.2 PNA FISH®

Peptide Nucleic Acid Fluorescence In Situ Hybridization (PNA FISH®) is a new method for the identification of bacteria and yeasts in blood culture within hours. This novel technology is based on a fluorescence in situ hybridization assay using peptide nucleic acid probes targeting 16S rRNA including *Staphylococcus aureus* (91). PNA fish gives rapid, highly sensitive and specific results to the physician within ~3 hours after blood cultures turn positive. This important information leads to a better and earlier treatment selection. It is easier and cheaper to perform than real-time PCR.

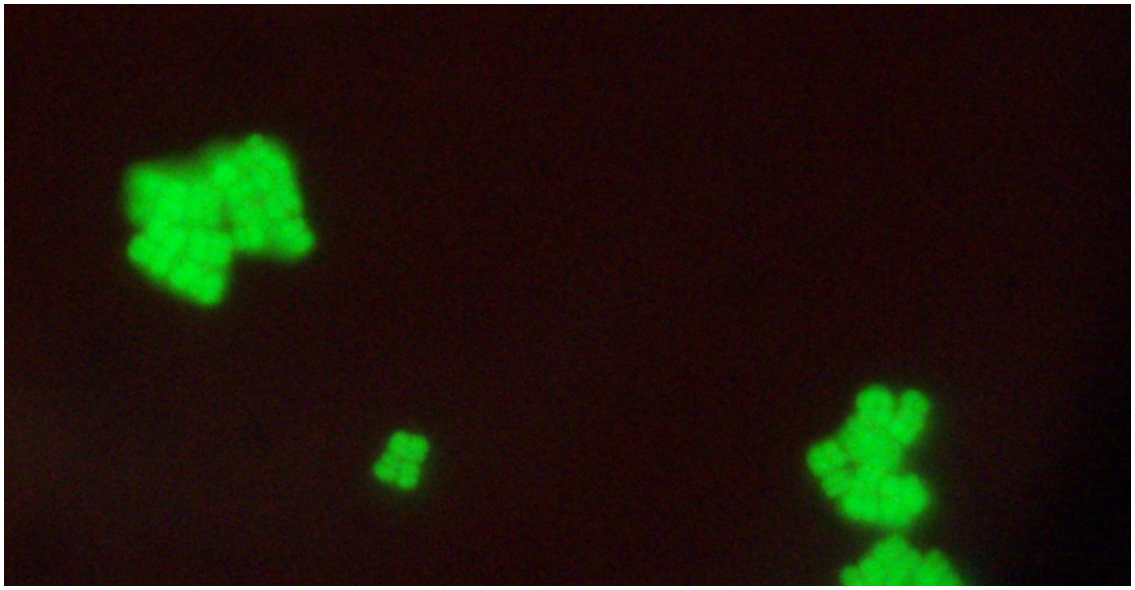
Forrest et al. conducted a study and showed that rapid differentiation of *S. aureus* from *coagulase negative staphylococci (CoNS)* in blood culture by PNA FISH® reduced length and cost of hospital stay, lead to an reduction of antibiotic use and early break up of vancomycin therapy in patients with a blood culture positive to *CoNS* (92).

In an article published by Oliveira et al., 87 *GPCC (gram positive cocci in clusters)* were identified directly from blood culture bottles, the diagnostic specificity, sensitivity and positive and negative predict values of *S. aureus* were 100%, 97%, 100% and 98% for *S. aureus* PNA FISH® compared to conventional methods (93).

González et al. demonstrated a 99.6% correlation between PNA FISH® test for *S. aureus* and the conventional methods used. The specificity and sensitivity results were similar to those obtained by Oliveira et al. (specificity 99.4%, sensitivity 100%) (93,94).

Another study published by Oliveira et al. in 2003 evaluating PNA FISH by using three different blood culture media, concluded that PNA FISH® is a rapid and solid method for detection of *S. aureus* in blood cultures. The sensitivity and specifity in this study were 100% and 99.2% (95). The advantages of PNA FISH® are the rapid results leading to reduction of inadequate antibiotic use. This might prevent emergence of resistance and reduce costs for treatment of SAB (92). *S. aureus* is identified as green fluorescing cell, *coagulase- negative staphylococci* as red fluorescing cells, while other species show no fluorescence (Figure 6) (95,96).

Figure 6. Green fluorescing cells (*S. aureus*)



1.11.2.3 BinaxNOW® for *S. aureus* and PBP2a

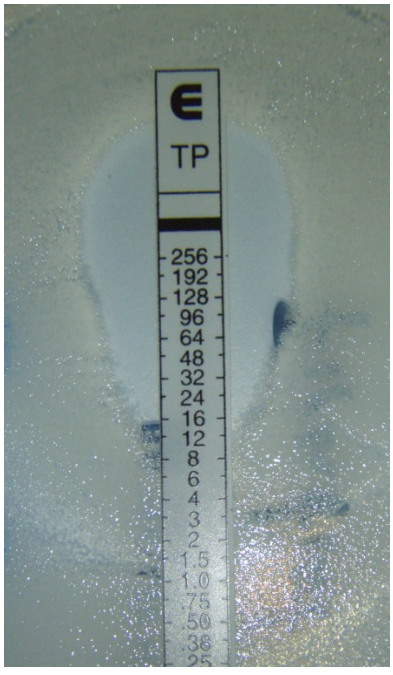
Rapid detection of MSSA and MRSA is important to provide adequate antibacterial treatment in time. The Binax Now® *S. aureus* test and PBP2a are two rapid immunochromatographic membrane assays that use sensitive polyclonal antibodies to detect *S. aureus* specific protein and penicillin binding protein 2a (PBP2a) directly from blood cultures positive with gram positive cocci in clusters. The results are available in 30 minutes from positive blood cultures, with high sensitivity and specifity in both tests, according to the distributor Alere International Sárl. There are no peer-reviewed studies published yet concerning BinaxNow® for *S. aureus* and PBP2a (97). Wilson et al. presented a poster at Australian society of for Microbiology annual scientific meeting 2011. They compared 121 blood culture isolates tested by culture and BinaxNOW antigen kits. The sensitivity for BinaxNow *S. aureus* kit was 92.6%, specifity 100%, positive and negative predictive values (PPV, NPV) 100% and 96%. For BinaxNow PBP2a sensitivity, specifity, PPV and NPV were 100%. BinaxNow *S. aureus* kit missed 3 from 29 methicillin sensitive *S.aureus* giving the kit a sensitivity of 90% for identification of *Staphylococcus aureus*. Their preliminary data suggest that a combination of BinaxNOW *Staphylococcus aureus* and BinaxNOW PBP2a is a good assay for detecting MRSA in blood cultures. They concluded that a positive BinaxNOW *Staphylococcus aureus/*BinaxNOW PBP2a results allow a rapid identification of MSSA and MRSA, this is very beneficial to patient treatment and outcomes (98).

1.11.3 Antimicrobial susceptibility testing

Antimicrobial susceptibility testing is used to determine in vitro susceptibility of bacteria to concentrations of antibiotics and can be done by diffusion or dilution methods. The susceptibility of an isolate to a certain antimicrobial agent is measured by establishing minimum inhibitory concentration (MIC). MIC is defined, as the lowest concentration of an antibiotic that will inhibit the visible growth of an isolate after overnight incubation.
The methods most commonly employed for sensitivity testing by disc diffusion, broth dilution or E-Test. In disc diffusion testing, a filter paper disc that contains a defined amount of different antimicrobial agent is placed on the surface of an agar plate (such as

Mueller-Hinton) that was previously inoculated with the bacterium that is going to be tested. After incubation, a zone of inhibition in the immediate surroundings of a disk portends susceptibility to that antibiotic. By using standard control stains the size of zone can be related to the MIC and results interpreted as whether the organism is susceptible (S), intermediately susceptible (I), or resistant (R) to that antibiotic. Susceptible is defined a bacterial strain inhibited in vitro by an antibiotic in adequate concentration resulting in a high therapeutic effect. Resistant is a bacterial strain inhibited in vitro by an inadequate antibiotic resulting in therapeutic failure. Intermediate is a bacterial strain inhibited in vitro by a concentration of antibiotics resulting in an uncertain outcome of treatment. Another diffusion method is to use an antibiotic gradient strip that creates an ellipse shaped zone of inhibition after incubation, the MIC is marked there where the growth intersects the strip (E-Test) (Figure 7). Both of these tests can be done manually or by instrument read (15).

Figure 7. E-test for determination of MIC



1.12 Resistance profiles

Antibiotic resistance or drug resistance enables a microorganism to survive exposure to an antibiotic inability of a pathogen to inactivate an antibiotic (77). The broad use of antimicrobial agents in hospitals, healthcare institutions and the outpatient setting promotes the emergence of multiresistant organisms. *S. aureus* has the ability to acquire resistance to some. The basis for antibiotic resistance and virulence of *S. aureus* is the accessory genome, that represents 25% of the whole *S. aureus* genome and barriers agile elements, like cassette chromosomes, plasmids, transposons, genetic islands and bacteriophages (99). Shortly after massive implementation of penicillin, the first penicillin resistant *S. aureus* strains, so called beta-lactamase producer (a penicillin deactivating enzyme), were introduced in the 1940s (100). Today more than 70-95% of *S. aureus* isolates from blood cultures are resistant to penicillin and ampicillin (68). Semisynthetic penicillin's (e.g. methicillin and oxacillin) that are only not hydrolysed by the staphylococcal penicillinase were used effectively as but 1961 the first Methicillin-resistant *S. aureus* (MRSA) has been reported (9,101). The *mecA* gene, which encodes the penicillin-binding protein PBP2a, is the genetic basis of resistance to all beta-lactam antibiotics including methicillin (102). MRSA has become even more prevalent over the years and is now endemic in some hospitals and also causing nosocomial outbreaks. The overall MRSA-rate has been reported to be around 30% of all *S. aureus* bacteremia, but the rates differ between hospitals and countries (103,104). Annual rates of methicillin resistance among invasive *S. aureus* isolates are currently decreasing or remain stable in most European countries, as reported by the European Antimicrobial Resistance Surveillance System between 2006 and 2009. However, in contrast to the general decreasing trend, rates of MRSA infection are still above 25% in 10 out of 28 countries. Malta reported the highest rate of MRSA isolates, reaching up to 58.1% in 2009. Austria shows a downward trend, the percentage of MRSA was 5.9% in 2009 compared to 9.1% in 2006. The decrease over the last years reflects collective long-term effort for MRSA control in hospitals (105).
The Surveillance Network–USA, an electronic surveillance network that reports resistance trends, shows that annual rates of MRSA have increased up to 59.2% in all regions of the United States during 1998-2005 (106).

The higher mortality rate among patients with MRSA bacteremia than MSSA bacteremia

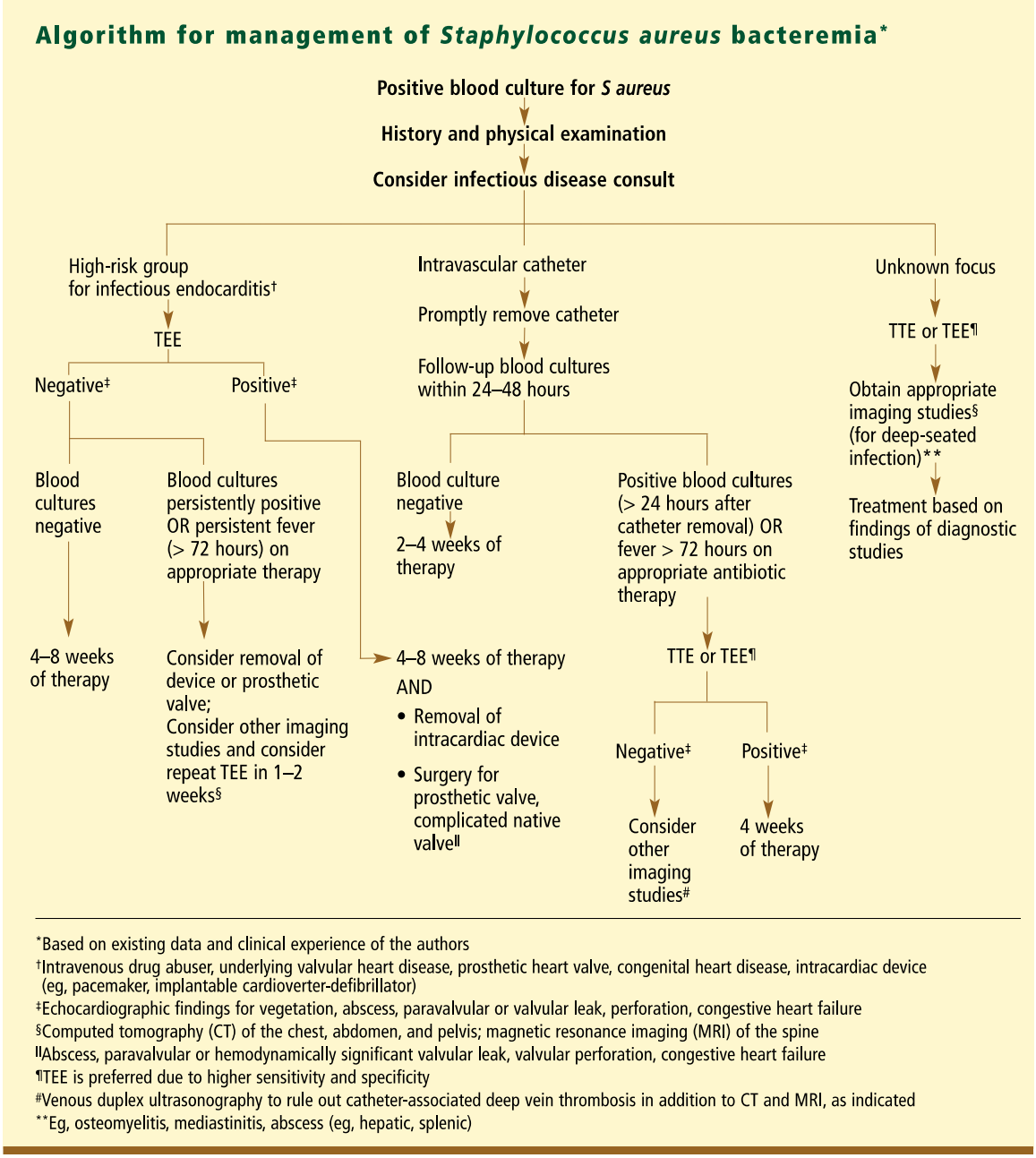
has been studied extensively (107,108). Cosgrove et al. conducted a meta-analysis in order to summarize the impact of staphylococcal methicillin resistance on mortality. Thirty-one cohort studies that contained information about reported numbers and mortality rates for patients with MRSA and MSSA bacteremia from 1980 to 2000 were included in the meta-analysis. A significant increase in mortality associated with MRSA bacteremia was observed, when all studies were combined (OR 1.93; 95% CI, 1.54-2.24; $p<0.001$). Only seven studies showed a statistically significant difference in mortality and in 27 studies an increased mortality in patients with MRSA bacteremia was evident. Even when adjustments were made for comorbidities or severity of illness an increased mortality was concluded (71). The Charlson comorbitiy score, severity of illness score and APACHE II are often used to measure the severity of illness and comorbidities in patients, but there is still a great diversity in these indices used in clinical research (109,110).
The management of MRSA bacteremia is a growing clinical challenge because of the lack of consensus on how to estimate underlying patients' comorbidities and select ideal antibiotic treatment (111).

Vancomycin, a glycopeptide antibiotic that inhibits bacterial cell wall biosynthesis, has been the major drug for treatment of MRSA infections for the past 40 years. However, in 1996, first case of *S. aureus* strains with decreased susceptibility to vancomycin (VISA – "vancomycin-intermediate *staphylococcus aureus*", MIC 4-16 μg/ml) was described. Another *S. aureus* strain is hetero VISA (susceptible to vancomycin when tested with routine susceptibility testing, but higher MICs of ≥4μg/mL) (112,113). Vancomycin resistant *S. aureus* strains (VRSA, MIC ≥16μg/ml) emerged by incorporation of the *vanA* operon from an *Enterococcus faecalis* strain into *S. aureus*, was first reported in 2002 in the United States (114). Nevertheless, high level vancomycin resistance in *S. aureus* is rare (115). Several new antibiotics (linezolid, daptomycin) with activity against MRSA have been licensed in the past few years.

1.13 Managment of *S. aureus* bacteremia

The optimal strategies for *S. aureus* bacteremia treatment are still a matter of much debate. Antibiotic therapy is initiated even with a single positive blood culture for *S. aureus*. Follow-up blood cultures should be obtained and the source and extend of infection determined by diagnostic measurements. The removal of intravascular foci is crucial for prevention of recurrence and infectious disease consultation should be considered.

Figure 8. Algorithm for management of SAB (by Kim and collegues) (60)



1.13.1 Antibiotic therapy for SAB

The rational selection and duration of antibiotics for SAB depends upon of following factors:

- Antimicrobial susceptibility (MSSA, MRSA and additional mechanisms of resistance)
- Mechanical predisposing factors (e.g. intravenous foreign material, prosthetic material)
- Predisposing host factors (e.g. patients age, predisposing valvular abnormalities, immunodeficiency, drug allergies)
- Evidence of complicated bacteremia
- Severity of illness on presentation

1.13.1.2 Drugs of choice

Penicillin is still the drug of choice for SAB where the isolate is susceptible to penicillin (MSSA), nevertheless <5-20% of isolates are sensitive to penicillin.
Beta-lactam antibiotics, like nafcillin or oxacillin (or flucloxacillin) (116) are the optimal therapy for isolates with a pencillin resistance. Cephalosporins, such as cefazolin are used for treatment of SAB in patients with penicillin allergy without a history of anaphylactic reaction (27). Vancomycin is currently recommended for the treatment for MRSA bacteremia, but it is less effective than beta-lactam antibiotics against MSSA infections. Chang et al. conducted a prospective multicentre study on 505 patients with MSSA bacteremia. They reported lower relapse rates and lower microbiological failures in patients treated with nafcillin (4%) compared to vancomycin (20%) (11). In another study 27 cases of bacteraemic MSSA treated with vancomycin were compared to 267 patients treated with nafcillin. Vancomycin treatment was associated with a higher mortality than those treated with nafcillin (37% vs. 18%) (117). Other observational studies and clinical trials have also reported about the negative effect of vancomycin therapy on patients

outcome, even if there is a changed from vancomycin to beta-lactam antibiotic therapy afterwards (118-120). Therefore glycopedptides, e.g. vancomycin are suggested just in cases of serious allergies or other absolute contraindications to beta-lactams (121).

A newer glycopeptide antibiotic is teicoplanin, it has demonstrated similar clinical efficiency in the treatment of MRSA infections as vancomycin, but showed fewer side effects. Teicoplanin is not licensed in the United States (122,123). Svetitsky et al. reported the efficacy and safety of vancomycin versus teicoplanin for infections caused by gram positive bacteria. They showed that there was no significant difference between teicoplanin and vancomycin concerning all-cause mortality and microbiological or clinical failure. They also concluded, that vancomycin had a higher incidence of nephrotoxicity and red man syndrome (124).

Daptomycin is a cyclic bacterial lipopeptid that has approved by the Food and Drug Administration in 2006 for the treatment of SAB and right-sided endocarditis. In clinical trials treatment with daptomycin of both MSSA and MRSA complicated skin and soft tissue infections and bacteremia with and without IE is demonstrated comparable efficacy and safety as conventional therapy. Of note, elevation of creatine phosphokinase (CPK) levels and development of resistance (MIC $\geq$2µg/mL) to the drug in patients treated with daptomycin have been reported (125,126).

Rifampin is a potent drug against *S. aureus*, but it is only recommended as a combination partner with e.g. gentamicin and vancomycin or antistaphylococcal beta-lactams for treatment of foreign-body associated infections such as prosthetic-valve endocarditis. Monotherapy with rifampin leads to rapid emergence of resistance (127,128).

Linezolid, quinupristin/dalafopristin, trimethoprim-sulfametoxazole, fluroquinolones, clindamycin or minocycline are alternative agents used for treatment of patients with contraindications against beta-lactams and vancomycin. These drugs have a lower efficiency because of resistance development or lower antistaphylococcal activity (128).

1.13.1.3 Dosage

Following dosages are recommended for the treatment of SAB (111,129)

- Penicillin G: 4 million units every 4 hours (up to 30 million units per day are recommended)
- Nafcillin or oxacillin: 2g iv. every four 4 hours, Flucloxacillin 2-4g iv. every 8 hours
- First generation cephalosporine (e.g. cefazolin): 2g iv. every 8 hours
- Daptomycin: 6 mg/kg iv. every 24 hours
- Vancomycin: 15-20 mg/kg iv. every 12 hours, in seriously ill patients, a loading dose of 25-30mg/kg can be used. Vancomycin serum trough levels must be monitored during treatment.

Lower doses of are often associated with recurrence, metastatic seeding and higher mortality (50).

1.13.1.4 Duration of therapy

Long term treatment (≥4 weeks) for patients with SAB was recommended in the 1950´when antibiotic became available, because SAB was associated with complications, e.g. endocarditis (130). However, further studies concluded that treatment duration of 10-14 days is sufficient, especially in patients with catheter-associated SAB. A 1992 review of literature concluded that less than 10 days intravenous antibiotic therapy increases the risk of recurrence (131-133). A prospective study, conducted by Fowler et al. on 244 patients in 1998, published treatment recommendations were the duration of antibiotic therapy was determined by clinical findings (e.g. removable focus of infection, prosthetic material), surveillance blood cultures, transesophageal echocardiography (TEE) and use of beta-lactam antibiotics if possible. They suggested that 7-14 days iv. therapy was appropriate for patients with uncomplicated SAB and 4-6 weeks therapy for patients with complicated SAB (40).
Current guidelines for SAB treatment suggest a minimum 14 days iv. therapy for uncomplicated SAB and 4-6 weeks treatment for SAB with deep focus of infection (134-

137). A course shorter than two weeks in patients with low complication rates is not justified, because it is associated with higher relapse rates (27). Nevertheless, interpreting all this treatment recommendations, the patient individual characteristics and clinical setting should be regarded.

1.13.1.5 Route of administration

Parenteral therapy is in general the preferred route of administration for SAB treatment. Oral treatment can be used to complete a full course of therapy in patients who require outpatient follow-up treatment. Schrenzel et al. compared oral therapy with a fleroxacin plus rifampicin with conventional parenteral therapy with flucloxacillin or vancomycin in 104 patients with SAB. In patients who received parenteral therapy length of hospital stay was longer (23 vs. 12, p=0.006), but they showed fewer side effects than patients treated with oral drugs. Both groups of patients achieved similar clinical and microbiological cure (around 80%) (138). Advantages of oral therapy are the simplicity, the lower costs and avoidable intravenous catheters risks for patients. In contrast, parenteral therapy provides higher serum levels and is better tolerated than high doses of oral drugs needed to achieve these serum levels.

1.13.1.6 Combination vs. monotherapy

Antimicrobial combination treatment has been used to improve bactericidal activity and to prevent development of antibiotic resistance. Although combination therapy with beta-lactam antibiotics and aminoglycosides increased the killing of methicillin-susceptible *S. aureus* in vitro and in experimental models of endocarditis compared to monotherapy, the clinical outcome was comparable with the two approaches and the combination gentamicin and nafcillin was associated with higher incidence of nephrotoxicity (139,140).

The American Heart Association guidelines state that the addition of gentamicin for therapy of native valve IE should be considered optional (141). Cosgrove et al. conducted a randomized trial on 236 patients with SAB and native valve infective endocarditis. 116 patients received standard therapy (penicillin or vancomycin) plus low dose gentamicin, 120 patients were treated with daptomycin monotherapy. They noted a significantly higher

reduction of creatinine clearance in patients who received initial low dose gentamicin than in the other group (22% vs. 8%. p=0.005). They concluded that low dose gentamicin is nephrotoxic and should not be used routinely as part of therapy for SAB and native-valve infective endocarditis (142). Other drugs that are often used in the combination therapy of SAB are rifampin, fusidic acid and fluoroquinolones. Riedel et al. conducted a retrospective cohort study on 84 patients with native valve *S. aureus* IE. 42 patients were treated with addition of rifampin to standard therapy and 42 controls (only standard therapy). Patients who were treated with addition rifampin more commonly had left-sided endocarditis and more often received gentamicin, otherwise they were similar to the control group. They found addition of rifampin to standard therapy was associated with longer duration of bacteremia (median 5.2 vs 2.1, $p<0.001$), lower survival rates, more frequent drug interactions, and hepatotoxicity (127).

1.13.1.7 Follow-up blood cultures

Follow-up blood cultures in *S. aureus* bacteremia are mandatory for monitoring treatment success. Chang et al. recommends drawing follow-up blood cultures in patients with SAB three days after starting antibiotic treatment. If the blood cultures remain positive, there is a higher risk for developing endocarditis, even if the echocardiography is negative. The follow-up blood cultures at day 3 after initiation of therapy are a good monitoring method that supports decisions on management strategies concerning antibiotic and surgical therapy in patients with endocarditis. There is no need to draw ensuing blood cultures as long as there are no signs of metastatic infections, fever, hypotension or symptoms of antibiotic inefficiency (21).

1.13.1.8 Diagnostic measures

Antibiotic treatment alone in SAB patients is not enough, as metastatic infection, endocarditis and the colonisation and infection of indwelling foreign material is commonly encountered. Background factors such as advanced age, metastatic complications, unknown primary focus, infected foreign devices and underlying comorbidities, are

associated with high mortality therefore it is important to identify them in order to optimize treatment (24,143). Patient's history and physical examination in addition to radiographic imaging studies performed based on the symptoms and echocardiography can help to identify metastatic foci.

Ringberg et al. conducted a study on 68 patients with SAB from November 1988 to June 1992. They evaluated the results of comprehensive diagnostic monitoring for metastatic complications. Chest X-ray, echocardiography, bone scintigraphy and leucocyte scintigraphy were performed to detect metastatic complications and endocarditis in patients. 53% of the patients screened showed metastatic complications and 26% were found to have endocarditis. Twenty-three patients required surgical intervention because of the positive screening results (56). Infective endocarditis or metastatic infections appear in 20% to 26% in patients with vascular catheter associated SAB. Metastatic complications result in one-third of patients with SAB either from local extension of infection or from haematogenous seeding from a distant focus (56,59).

Transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) are essential for the diagnosis, classification and management of IE. These diagnostic tools can detect vegetations on valves and cardiac devices, identify abnormal valves and congestive heart failures (144,145). In many studies transesophagal echogardiography is recommended for detection of endocarditis in patients with SAB (59,146).

Bayer et al. conducted two studies to estimate the significance of different diagnostic methods for endocarditis and reported that echocardiography had the highest validity (147,148). TTE is the first option in patients with low risk for endocarditis it is more widely available, less invasive, easier and cheaper to perform than TEE (141,149,150).

An additional TEE is recommended for patients with complications or high clinical expectation of IE, or where TTE imaging is difficult (134). TEE is also indicated in patients with prosthetic heart valves. However, TEE is more sensitive than TTE in identifying complications of IE, like valvular vegetations, prosthetic valve endocarditis or abscesses. TEE can detect vegetations smaller than 8mm (151,152). Some studies reported sensitivity for TTE of 17% to 36% and for TEE 82% to 96 % in patients with prostehtic valve vegetations (153-155).

1.13.1.9 Removal of the original focus

Removal of infected intravascular devices is essential in addition to antibiotic treatment in the management of SAB, because retention is frequently associated with relapse. A study showed that in 50% of patients an intravascular device was the source of infection in both hospital and community acquired SAB (156). In a study conducted by Fowler et on 244 patients with SAB, infected foreign bodies were not removed in 23 patients, 56% of them developed recurrence, compared 16% of 221 patients who did not have a device or where the device was not removed ($p<0.01$) (40). Chamis et al. found that patients with cardiac devices (permanent pacemakers or implantable cardiac defibrillators) and SAB had a high risk for relapse and an increased mortality, if the device was not removed (157). Based on this and other studies, it is recommended to remove all intravascular devices if possible in patients with SAB. Surgical intervention in patients with left-sided endocarditis is indicated if antimicrobial treatment fails and criteria like congestive heart failure, myocardial invasion, high grade valvular insufficiency or high risk for embolic complications are met (141). In several studies surgical therapy for patients with *S. aureus* IE was associated with significant long-term survival benefit compared to medical management alone (158-161).

1.13.1.10 Impact of Infectious disease consultation (IDC)

Infectious disease consultation has been associated with improvement in the management and the outcome of SAB. Recent studies have shown that IDC has an impact on the optimal selection of management strategies that lead to cure and lower relapse rates (40,41,44,162). However, data are limited and the effect on outcome is unclear.

Fowler et al. recommended IDC to 244 patients with SAB at the Duke Medical Center. Patients were followed for 12 weeks after their first blood culture positive for *S. aureus*. In 112 patients management recommendations were accepted, compared to 132 patients were recommendations were partially followed or completely ignored. Patients whose physician adhered to recommendations were associated with lower relapse rates (6.3% vs. 18.2%; $p<0.01$) and were more likely to be cured of their infection (79.5% vs. 64.4%; $p<0.01$)

compared to those where recommendations were not followed. There was no statistical significant between patients with and without IDC concerning mortality rate (40).

Another recent retrospective cohort study performed by Jenkins et al. compared outcome, management and patients characteristic before (n=127) and after (n=98) implementation of routine IDC. Patients receiving IDC were associated with a significant improvement of all standards of care (e.g. removal of intravascular foreign bodies, follow up blood cultures, use of parenteral beta-lactam antibiotics, adequate treatment duration) compared to those where IDC was not adhered to (40% vs. 74%; $p<0.001$). Without IDC, no patient had met all 4 standards. Performance of echocardiography increased from 57% to 73% ($p=0.01$), IE and metastatic infections were diagnosed more often (33% vs. 46%; $p=0.04$) and intravascular catheters were removed more frequently (92% vs. 67%; $p=0.001$) during the period of routine IDC. There was no statistically significant difference concerning overall mortality and recurrence of bacteremia (41).

A reduction of the length of hospital stay and 28-day or 30 day mortality in patients with SAB receiving IDC routinely or by request of the attending physician were reported in some recent studies. There is a consensus in all these studies, that ID consultation should be performed in patients with SAB whenever possible (162-165).

Aims of the study

The objective of our study was to determine the impact of routine infectious diseases service consultation on the evaluation, management, and outcome of *Staphylococcus aureus* bacteremia, especially:

1. To investigate the effect of routine infectious disease specialist consultation on adherence to SAB standards of care
2. To explore the influence of routine infectious disease specialist consultation on mortality due to SAB and
3. To investigate the influence of different levels of applied SAB standards of care on mortality due to SAB.

2. Patients and Methods

2.1 Setting and study design

From January 2008 until July 2010 all patients with isolation of *Staphylococcus aureus* from blood cultures hospitalized at the Department of Internal Medicine at the Medical University of Graz, Austria were included and followed prospectively. Data were collected using a standardized data collection form (see Appendix) and hospital computerized database MEDOCS. Routine IDC was implemented in November 2008, but some patients from earlier periods had received IDC on demand. The standards of care met with and without IDC were compared.

2.2 Study population

Patients with one or more blood cultures positive for *Staphylococcus aureus* and with clinical evidence of infection were included in the study. Patients with SAB relapse were included a second time only if they were discharged from hospital after the first episode, a positive follow-up blood culture did therefore not count as a second episode. For the analysis of baseline data and risk factors, all patients were included. For analysis of the standards of care met and survival, patients who died within three days after blood culture was drawn, were excluded.

2.3 Data collection

Medical records and charts of the patients were reviewed and collected from the hospital database on the standardized questionnaire form (see Appendix) and stored in a database. Data analysis was performed using the statistical package for social sciences (SPSS) version 17. Items recorded for each patient included: sex, age, underlying diseases, Charlson co-morbidity score, severity of illness score, predisposing factors and risk factors (e.g., immunosuppression, indwelling catheters, concomitant medication, medical

procedures before onset), previous hospitalization, length of hospital stay, the suspected or microbiologically proven source of bacteremia, SAB classification, clinical parameters at SAB onset, microbiological data (antimicrobial susceptibility, differential time to positivity if applicable) and the standards of care (e.g., adequate antimicrobial agent and duration, TEE or TTE, removal of intravascular foreign material like CVC). All patients were followed for 360 days after positive blood culture draw. Survival data were collected from the county-wide hospital data base and using a local internet obituary database.

2.4 Management standards and case definitions

Using international guidelines and results of prior studies, five standards of care for SAB were measured in our patients (40,41).

1) Removal of an intravascular focus of infection, if present, within 4 days
2) Obtaining follow-up blood cultures 2-4 days after onset of SAB
3) Use of parenteral beta-lactam antibiotics for methicillin-susceptible infections
4) Adequate duration of treatment
    a. Administration of at least 28 total days of therapy for treatment of complicated SAB
    b. Administration of at least 14 days of therapy for uncomplicated SAB
5) Performance of TTE or TEE

Following definitions were used in the study:

Hospital acquired bacteremia

The index blood culture was drawn after 72 hours of hospitalization and there were no clinical signs of SAB at the time of admission

Community acquired bacteremia

The index blood culture was drawn within 72 hours and signs consistent with SAB were present on admission.

Health care associated bacteremia

A blood culture positive within 72 hours of hospitalization in a patient with clinical signs of bacteremia who received haemodialysis, outpatient iv. treatment, previous hospitalization within a month prior to admission)

Uncomplicated bacteremia and Complicated bacteremia

Classified according published definitions, as described above (40).

Severity of illness score

Estimate patient´s mental status, the presence of fever, recipient of mechanical respiratory support and cardiac status.

Charlson comorbidity score

An estimate of patients` prognosis in longitudinal studies according to their accompanying diseases as described by Charlson et al. (109)

Endocarditis

Was defined according the modified Duke criteria, as described above (61).

Source of infection

The source of infection was determined by the presence of clinical signs and symptoms for infection or isolation of *S. aureus* at a site of infection. Intravascular catheter associated SAB was defined by evidence of catheter inflammatory signs and/or positive quantitative culture results for *S. aureus* of catheter material and no evidence of any other focus. For CVCs or Port a Caths a differential time to positivity of > 2 hours was also used to define catheter related blood stream infection. Bacteremia was considered as 'unknown source' when the source of infection could not be identified.

Adequate antibiotic treatment

Appropriate antibiotic treatment was considered as a treatment with antistaphylococcal beta-lactam for MSSA or vancomycin for MRSA, given intravenously for at least 7 days for uncomplicated bacteremia of at least 14 days for complicated bacteremia at an adequate dosage. Total treatment duration was considered adequate if a minimum of 14 days for uncomplicated bacteremia or a minimum of 28 days for complicated SAB was achieved.

Recurrence

Relapse of SAB was defined as re-admission with positive blood culture after clinical improvement and discharge.

ID consultation adherence

ID consultation was performed upon requested by the primary physician in charge or automatically after implementation of routine IDC. All ID consultations routinely advised to meet the five standards. Adherence to ID recommendations was measured using the five standards of care that were actually met.

2.5 Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) software (version 17; SPSS: Chicago, IL, USA). Categorical variables were compared using either Pearson´s chi-square test or Fisher´s exact test, as appropriate. Kaplan-Meier estimates were used to calculate survival curves. The log rank test was used to test for statistical significance of survival. A p value ≤ 0.05 was considered to indicate statistical significance. Statistical tests were mainly used to predict the impact of IDC on

1) Removal of intravascular devices (if present)
2) Adequate duration of treatment
3) Use of beta-lactam antibiotics for MSSA
4) Follow- up blood cultures
5) Echocardiogram preformed
6) Survival

3. Results

3.1 Patients

During the study period a total of 138 patients with SAB were identified. Nine patients were excluded for the analysis of standards of care met because they already died within 3 days after blood culture draw. Out of the remaining 129 patients with SAB, IDC was performed in 90 (79.7%) patients. Out of all 138 cases, 136 were caused by MSSA (98.4%) and 2 (2.6%) by MRSA. Within those who were eligible for standards of care analysis, only one patient had an MRSA isolated. The other MRSA patients died within the first three days after positive blood culture was drawn. The median age of the patients was 64 years (range 18-92), 85 cases (61.6%) of SAB were male and 53 cases female. 89 (69%) patients were primarily admitted to a medical ward, 9 (7%) patients were to a surgical ward, 18 (14%) were admitted to an Intensive Care Unit and the remaining 15 distributed to other wards. In our study 54 (39.5%) cases of SAB were classified as health care associated 41 (29.7%) cases were hospital acquired and 43 (31.2%) community acquired. Microbiologically proven relapse occurred in 10 patients (7.2%). There was no statistical significant difference between patients with and without IDC concerning sex (p=0.515), age (p=0.994) and severity of illness score (p=0.852). The Charlson comorbitity index was comparable in both groups. (Cramer's V p=0.332). Patients' demographic characteristics and risk factor distribution are shown in Table 3 and 4, and didn´t show any statistically significant differences.

Table 3. Patients' demographic characteristics (including only 129 patients eligible for standards of care analysis)

Variable	IDC (n=90)	No IDC (n=39)	p-value
Age	63.0	61.8	0.994
Male gender	54	24	0.515
Primary admission			0.423
non-ICU	74	37	
ICU	16	2	
Type of SAB			
CA	32	6	
HCA	31	20	
HA	27	13	
Source of bacteremia*			0.760
Unknown	2	1	
Foreign bodies	44	23	
Skin and/or soft tissue	28	8	
Respiratory tract	5	1	
Other	11	6	
Complicated SAB	54	21	
Uncomoplicated SAB	36	18	

ICU: Intensive care unit; CA: community acquired; HCA: health care associated; HA: hospital acquired;
* analyzed retrospectively

Table 4. Risk factors of SAB patients, with and without IDC

Risk factor	IDC (n= 90) No. (%)	No IDC (n= 39) No. (%)	p-value*
Underlying diseases			
Solid tumor	19 (14.7)	11 (8.5)	0.098
Cardiovascular disease	51 (39.5)	19 (14.7)	0.405
Haemodialysis	20 (15.5)	14 (10.9)	0.105
Chronic lung disease	16 (12.4)	9 (7)	0.484
Diabetes mellitus	22 (17.1)	12 (9.3)	0.454
Liver cirrhosis	4 (3.1)	3 (2.3)	0.536
Decubital ulcerations	9 (7)	7 (5.4)	0.208
Neutropenia	6 (4.7)	1 (0.8)	0.339
Medical immunosuppression	22 (17.1)	9 (7)	0.867
HIV	0 (0)	0 (0)	
Charlson comorbitiy index			0.332
0	13	5	
1-3	18	5	
4-7	48	19	
> 7	11	12	
Severity of illness score			0.852
0	5	2	
1-3	66	27	
> 3	19	10	
Medical devices and procedures			
Intravascular foreign bodies**	17 (13.2)	6 (4.7)	0.264
Orthopaedic devices	12 (9.3)	3 (2.3)	0.502
Prosthetic vascular accesses	5 (3.9)	2 (1.6)	0.883
Central dialysis access	15 (11.6)	12 (9.3)	0.324
Peripheral iv. access	28 (21.7)	13 (10.1)	0.803
iv. injection	16 (12.4)	5 (3.9)	0.484
Central venous lines within 3 months	16 (12.4)	15 11.6)	0.100
Paravertebral infiltration	5 (3.9)	2 (1.6)	0.922
Small surgical procedures	5 (3.9)	4 (3.1)	0.086

* Chi- square test; ** at onset excl. central venous catheter

3.2 Impact of IDC on standards of care

Patients who received IDC were associated with a significant improvement of all standards of care as shown in Table 5. Removal of intravascular foreign bodies was more commonly performed in patients with IDC than in patients without IDC (95% vs. 67%, $p<0.009$), adequate treatment duration improved (88% vs. 30%, $p<0.001$), the use of a antistaphylococcal beta-lactam for MSSA were used more commonly in patients with IDC

(97% vs. 68%, p<0.0001), follow up blood cultures were obtained more frequently (88% vs. 26%, p<0.001) and echocardiograms were done more frequently (87% vs. 18%, p<0.0001). The cumulative number of standards met per patient was also significantly increased (p<0.001). No patient had met all standards of care without IDC (Table 6 and Figure 9). SAB recurrence was significantly lower in patients with IDC compared to patients without IDC (p=0.024) (Table 7). Patients with IDC showed a better survival than patients without IDC (log rank test p=0.028) (Figure 10).

Table 5. Impact of IDC on standards of care met

Basic standards	**Done/not done**	**IDC (n=90)**	**No IDC (n=39)**	**p-value**
Removal of CVC (if present)	Yes	35	14	<0.009
	No	2	7	
Adequate treatment duration*	Yes	71	10	<0.001
	No	10	23	
Antistaphylococcal beta-lactam for MSSA	Yes	86	26	<0.0001
	No	3	12	
Follow-up BC	Yes	80	10	<0.001
	No	10	29	
Echocardiogram preformed	Yes	78	7	<0.0001
	No	12	32	
Additional standards				
Combination treatment for indwelling foreign bodies	Yes	47	0	<0.001
	No	19	31	
Combination treatment for complicated SAB	Yes	49	3	<0.001
	No	5	18	

CVC: central venous catheter; BC: blood cultures; *excluding patients who died or were lost to follow-up, before adequate duration was achieved

Table 6. Number of standards met with and without IDC

	With IDC (n=90)	Without IDC (n=39)
no standard met	0	4
1 standard met	3	9
2 standards met	2	12
3 standards met	3	7
4 standards met	16	2
5 standards met	57	0

Figure 9. Number of standards of care met with and without IDC

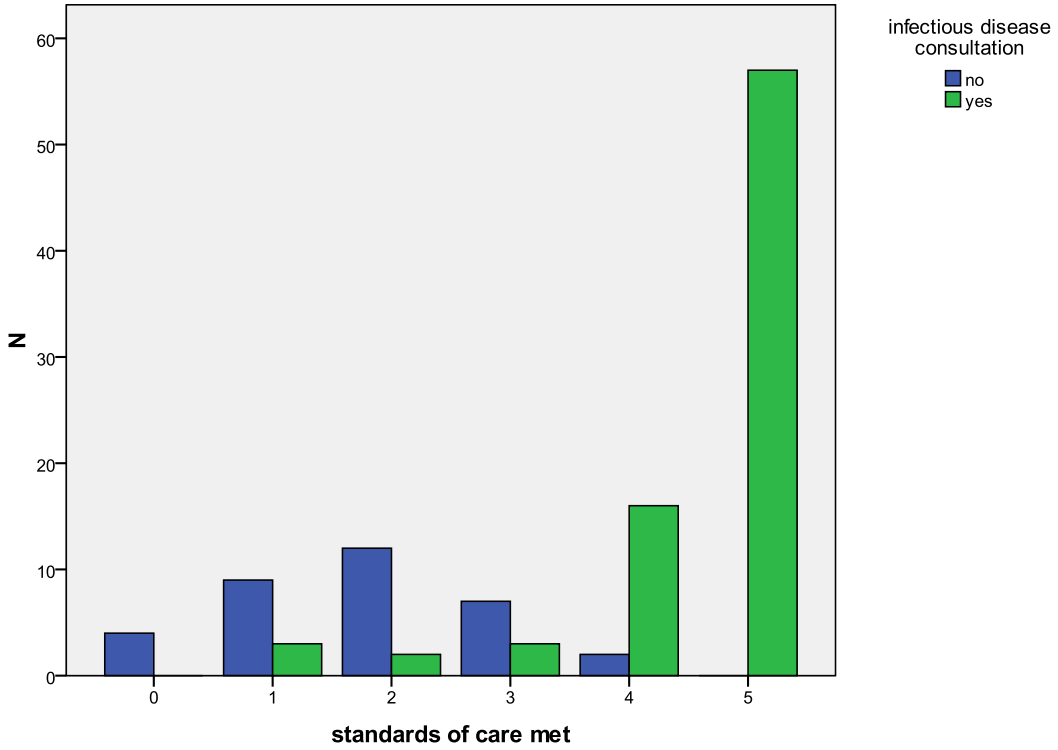
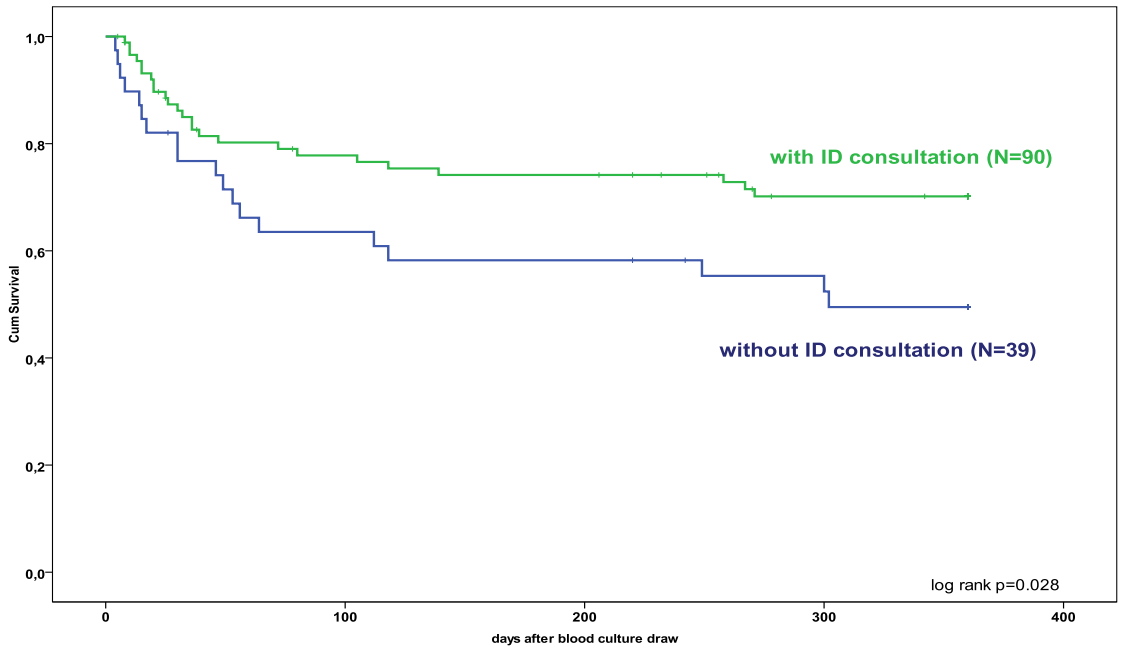


Table 7. Relapse of SAB with and without IDC

SAB relapse time	Within 1 month	1-2 months	3-6 months	6-12 months	>12 months	p-value
IDC (n=90)	2	0	0	1	4	0.024
No IDC (n=39)	8	1	2	0	0	

Figure 10. Impact of IDC on survival



4. Discussion

4.1 Impact of IDC on adherence to SAB standards of care

Staphylococcus aureus is a major pathogen causing community and hospital acquired bacteremia. Despite the availability of effective antibiotics, the mortality rate among patients with SAB has been described to be at 11-43 % (24,25).

The proper treatment of SAB is complex, because it carries a high risk of complications such as metastatic seeding, endocarditis, severe sepsis or relapse. Following standards of care is essential for the treatment and outcome of patients with SAB and consists of removal of infected foci, choice of adequate antibiotic therapy and appropriate duration, screening for deep seated infection or endocarditis by echocardiography and follow up blood cultures draw (11,137,141).

IDC has been associated with increased impact on the adherence of these standards of care. Similar to results of previous studies, we confirmed the value of IDC for improving the management and outcome of patients with SAB (40,41,44,163,165). Patients in our study who had an IDC were significantly more likely to receive adequate duration of treatment and appropriate antibiotic selection, removal of intravascular devices, follow up blood cultures and an echocardiogram performed. Jenkins et al. also described that IDC results in detailed evaluation of the patients and a more frequent recognition of metastatic infections and endocarditis, and improve adherence to standards of care. They did not show a significant impact of IDC on treatment failure, like recurrence or mortality (41). Our study differs from that of Jenkins et al. (41). The SAB population in their study had almost an equal distribution of MRSA and MSSA, in contrast to our study where only two cases of MRSA bacteremia occurred. In addition, they did not include the performance of echocardiography as a standard of care. In our study echocardiography was included in the standards of care and we could show that performance of this diagnostic measure improves with IDC. This is important, because echocardiography can play a central role in the diagnosis of IE, as recommended by the American Heart Association that echocardiography should be performed in all patients with suspected IE (141).

Follow up blood cultures were significantly more frequently obtained in patients with IDC than those without IDC, this is concordant with other studies (41,142).

Several prospective studies have shown that inappropriate antibiotic treatment is known to have detrimental effects and is a significant risk factor for mortality resulting from SAB (166,167). In our study, we could not show that inappropriate treatment has an effect on the mortality of SAB patients, because the number of patients who received inappropriate treatment (e.g. did not receive a beta-lactam) was too small. The reason for this fact is the low MRSA rate at the University hospital of Graz and the frequent use of empiric beta-lactams with antistaphylococcal activity. We could show that adequate duration of treatment was significantly increased by routine IDC.

Combining antibiotics to enhance bacterial killing in patients with complicated bacteremia, has never been shown to improve outcome (127,142), but has been widely used. Rifampin based combinations are recommended for the treatment of staphylococcal foreign body infections by the Paul Ehrlich Gesellschaft für Antimikrobielle Therapie 2010.

In our study patients receiving IDC were more often treated with combination therapy for indwelling foreign bodies and complicated bacteremia. The most commonly used combination partners were rifampin and fucidic acid.

4.2 Impact of IDC on mortality due to SAB

Recent studies, from different regions of the world (163,165,168) reported lower mortality rates in patients with SAB who received IDC in addition to better adherence to standards of care and recommendations. However, long term survival data have not been presented. Our data did not show lower rates of in hospital mortality, but a long term survival benefit (Table 8).

Table 8. Impact of IDC on outcome of SAB in present and recent studies

	Design	Patients	Relevant observations	All-cause mortality (IDC
Nagao et al. (168)	Retrospective cohort study	346	↑follow up blood cultures, ↑adequate antibiotic therapy, ↑ TEE/TTE	30-day 16 vs. 26% (p=0.04)*
Lahey et al. (165)	Retrospetctive cohort study	240	↑follow up blood cultures, ↑ removal of foreign bodies, ↑adequate antibiotic therapy	In- hospital 14 vs. 24% (p <0.01)**
Rieg et al. (163)	6 year cohort study	521	↑ adhrence to minimum treatment duration, ↑ TEE/TTE	In- hospital 19 vs. 28% (p= 0.03)**,a
Present study	Prospective cohort study	129	↑ removal foreign bodies, ↑follow up blood cultures, ↑ TEE/TTE	long term survival benefit (log rank p= 0.028)

↑: increase; TEE: transesophageal echocardiography; TTE: transthoracic echocardiography

* difference in mortality rates in patients with two different study periods

** significant in multivariable analysis as well. [a] significant also for 90 day all-cause mortality

Until recently, most studies failed to demonstrate a survival benefit in patients with SAB receiving IDC, they just have described a positive effect of IDC on the adherence to standards of care for management of SAB (40,41,44,162). In the study conducted by Fowler et al. mortality was slightly lower in the group where IDC recommendations were followed, however these findings just failed to reach statistical significance (40). Kaech and collaegues reported a reduction in mortality due to IDC during SAB in univariate but not in multivariate analyses (44). Further prospective studies are needed to evaluate the impact of IDC on mortality.

4.3 Impact of IDC on SAB relapse

Recently, Fowler and colleagues evaluated the clinical outcome of patients with SAB for whom IDC recommendations were followed. Recurrence occurred significantly less likely in patients with IDC and they were cured more likely of their infection than patients without IDC (40). A possible explanation may be that many patients without IDC received haemodialysis unlike those with ICD, who predominantly had more cases of endocarditis and metastatic infection at the onset of therapy.

In our study we also found a significantly lower rate of early relapse in patients with an IDC. Most of the patients, who relapsed in the IDC population, experienced their second SAB episode more than one year after the first SAB, which would be considered as re-infection and not relapse.

4.4 Limitations

There are several limitations of our study. First, patients included before implementation of routine IDC were evaluated retrospectively from the hospital computerized database MEDOCS. Therefore, for some patients at least, incomplete data sets were available, which were assessed very carefully. Second, patient follow-up after discharge from hospital was not available in some cases, so that there are missed relapses. Third, our population has a very low MRSA rate, so we cannot say if patients with SAB due to MRSA would derive a greater benefit from IDC than those from MSSA bacteremia. It is known from the literature that MRSA bacteremia has a higher mortality rate than MSSA bacteremia. Finally, we classified cases as complicated or uncomplicated according to published definitions, however uncertainty still exists regarding adequate classification of SAB. Additionally, there are also uncertainties concerning the optimal treatment of SAB, and the treatment guidelines suggested in literature cannot be applicable to all patients.

4.5 Conclusion

Our data show that infectious disease consultation is associated with significant improvement in the management of SAB. Mortality from SAB decreases as standards of care are being followed. IDC is associated with increased diagnostic evaluation, appropriate antibiotic selection removal of indwelling foreign bodies and improved adherence to standards of care. Routine IDC should be done in SAB whenever possible, especially in patients with complicated SAB.

5. References

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6. Appendix:

Bakteriämie-Evaluierung MiBi UKIM

Basisdaten

Nachname		Aufnahmedatum	
Vorname		Aufnehmende Station	
Geburtsdatum		Entlassungsdatum	
Patientennummer		Entlassende Station	
Grösse (cm)		Gewicht (kg)	
Geschlecht (W=0, M=1)			

Komorbiditäten

Solider Tumor		Nein (0)			
		Ohne Metastasen (1)		Welcher	
		Mit Metastasen (2)		ED	
Hämatologische Erkrankung (1/0)		Welche		ED	
SOT (1/0)		Welches		Wann	
KMT (1/0)		Welche		Wann	
CED (1/0)		Immunsuppression		ED	
Chron. Diarrhoe (1/0)[1]		Blutig		Seit	
Cardiovasculär (1/0)		CMP (1/0)		NYHA (1-4)	
		KHK (1/0)		MI (0=nein, 1=Z.n.; 2=akut)	
				Stent(0=nein; 1=alt; 2=aktuell vor SAB onset)	
		Vitium (1/0)		Welches	
		Z.n. IE (1/0)		Wann	
Chron. Lungenerkrankung		COPD (1/0)		Grad (1-4)	

[1] > 3 Monate

(1/0)					
		Asthma bronchiale (1/0)		Bronchiektasen (1/0)	
		Fibrose (1/0)		Interstitielle Lungenerkrankung (1/0)	
Chron. Hepatobiliäre Erkrankung (1/0)		Zirrhose		Seit	
				MELD	
				Child-Pugh (A=1; B=2; C=3)	
		Sonstige		Welche	
Chronische NINS (1/0)					
Chronische HD (1/0)		Seit			
		Cimino-Shunt (1/0)		Seit	
		Gefässprothese (1/0)		Seit	
		PermCath (1/0)		Seit	
Parenterale Ernährung (1/0)		Über (1=Venflon; 2=ZVK; 3=beides)		Seit	
Diabetes		Insulin		Seit	
		Diab. Fuss		offen	
Decubitalulcera		Wo		Seit	
Sonstige Diagnosen lt. FK oder AB					
Charleson Score		Age-adjusted:		Age-unadjusted:	

Severity of illness

Temp > 38 (1P)		Temp > 39 (2P)		P:
Alert (0P)		Disoriented (1P)		
Stupor (2P)		Coma (4P)		P:
Hypotension (2P)				P:
Mechanical respiratory support (2P)				P:
Cardiac arrest (4P)				P:
			Summe SOI	

Immunsuppression

Medikamentös		mit		seit	
		mit		seit	
		mit		seit	

Systemisch Cortison[2] (0=nein; 1=Dauertherapie; 2=Stoss und Taper)		Dosis[3]		von-bis	
Chemotherapie (1/0)[4]		mit		zuletzt	
		Vortherapien			
Antikörpertherapie jemals (1/0)		mit		zuletzt	
		mit		zuletzt	
HIV (1/0)		seit		CD4	
		Therapie			
Neutropenie (1/0)[5]		wegen		seit	
Antikörpermangel (1/0)		wegen		seit	
Bestrahlung (1/0)		Gebiet		zuletzt	

Medizinische Eingriffe (innerhalb 3 Monaten vor Aufnahme)

Art		**Datum**	**Anmerkungen**
Venflon (1/0)			
IV-Injektion (1/0)[6]			
ZVK-Anlage (0=nein; 1=Infusions-ZVK; 2=Dialyse-ZVK nicht-tunneliert; 3=Dialyse-ZVK tunneliert; 4=Hickman; 5=Port-a-Cath)			
Umstände der ZVK-Anlage[7]			
Intramuskuläre Injektion (1/0)			
Subcutane Injektion (1/0)			
Intraartikuläre Injektion (1/0)			
Ambulante parenterale Thp (1/0)			
Shuntanlage (0=nein; 1=Prothese; 2=Cimino)			
Kleine Chirurgie (1/0)[8]			
Abdominalchirurgie offen (1/0)			

[2] Innerhalb der letzten 4 Wochen vor SAB-Onset.
[3] Prednison-Äquivalent in mg/Tag bei SAB-Onset.
[4] Innerhalb der letzten 4 Wochen
[5] < 500 Neutrophile.
[6] Auch im Rahmen von KM-CT, MRT, Szinti etc.
[7] ICU-ZVK-Buch.
[8] Max. 2 Tage stationär oder ambulant

Trauma-Chirurgie (1/0)			
Gyn.Eingriff (1/0)			
Laparoskopie (1/0)			
Arthroskopie (1/0)			
Epidurale Schmerztherapie (1/0)			
Paravertebrale Infiltration (1/0)			
Urolgischer Eingriff (1/0)			
HNO-Eingriff (1/0)			
Zahnärztlicher Eingriff (1/0)[9]			
Endoskopie (0=nein; 1=ohne Venflon; 2=mit Venflon)			
Heimparenterale Ernährung (1/0)			
Interventionell-radiologischer Eingriff (1/0)			
Coronarangiographie (1/0)			
Schrittmacher-Anlage (1/0)			
IVDU (1/0)			

Health Care System Contact vor BSI-Onset

Hositalisiert innerhalb			wegen	Datum der letzten Entlassung aus stationärer Pflege
x in	30 Tagen (1)			
x in	60 Tagen (2)			
x in	90 Tagen (3)			
x in	120 Tagen (4)			Anmerkungen
x in	1 Jahr (5)			
Pflegeheim			Seit	

Dokumentierte (mögliche) Hinweise auf die spätere Diagnose zum Aufnahmezeitpunkt

Aus Anamnese	Aus klinischer Untersuchung

Quelle der Bakteriämie

[9] Mit Verletzung des Zahnfleisches

	Initial vermutet		Retrospektiv	
		Begründung		Begründung
Urogenital (1)				
Abdomen (2)				
Haut/Weichteil (3)				
Lunge (4)				
Knochen (5)				
Fremdkörper (s.u.) (6)				
Sonstige (7)				

Art der Bakteriämie[10]

HA-BSI		HCA-BSI		CA-BSI	

Liegende Fremdkörper bei BSI onset

		Wie lange	Äusserlich Hinweis auf Infektion	Anmerkungen	Entfernung (wann)
ZVKs (1/0)					
PermCath (1)					
Subclavia (2)					
Femoralis (3)					
Jugularis (4)					
Port-a-Cath (5)					
(6)					
Urogenital (1/0)					
Ureterkatheter (1)					
Suprapubischer Blasenkatheter (2)					
Nephrostoma (3)					
JJ-Stent (4)					
(5)					
Gastrointestinal (1/0)					
Colostoma (1)					
PEG-Sonde (2)					
Gallengangsstents (3)					
Nasogastralsonde (4)					
(5)					
Respirationstrakt (1/0)					
Endotrachealtubus (1)					
Tracheostoma (2)					
(3)					

[10] Nach del Rio et al, CID 2009:48; Suppl 4, S246

Intravaskulär (1/0)					
Künstliche Herzklappen (1)					Wo:
Gefässprothese (2)					Wo:
Schrittmacher (3)					
ICD (4)					
Cavaschirmchen (5)					
Coronarstent (6)					
Mehrere (7)					
(8)					
Orthopädisch (1/0)					
HTEP (1)					
KTEP (2)					
sonst. TEP (3)					Wo:
Intraossäres Metall (4)					Wo:
Mehrere (5)					
(6)					
Andere (1/0)					
Liquorshunt (1)					
(2)					

Mikrobiologie

Keim			MSSA	
			MRSA	
			ESBL	
	Erwartetes Antibiogramm nach Resistenzbericht[11]			
Datum der Abnahme				
Flaschenzahl	Gesamt		Positiv	
	Zentral		Peripher	
	DTP		Anmerkungen	
Gram-Präparat	Datum			
Antibiogramm	Datum			
Laborendbefund	Datum			
	Uhrzeit			
AOLC (1/0)	Datum			
	Uhrzeit			

[11] Nur für Gram Negative. Mehr als 50% Konkordanz zu mehr als 50% der getesteten Antibiotika für jeweiliges Bakterium aus Blutkulturen im Resistenzbericht des jeweiligen Jahres

PNA FISH (1/0)	Datum		
	Uhrzeit		

Bei CRBSI: Katheter entfernt?

Datum		Uhrzeit	
		Dauer der adäquaten Therapie bis zur Entfernung (h)	

Katheter belassen	

Spitze ins Labor gelangt (1/0)		Gleicher Keim (1)		
		Anderer Keim (2)		
		Zweiter Keim (3)		
		Keimzahl		

Mikrobiologische Vorbefunde (1 Jahr)

Späterer BSI-Keim zuvor identifiziert (1/0)	Ja		Nein	
Lokalisation 1		Datum 1		
Lokalisation 2		Datum 2		
Lokalisation 3		Datum 3		
Öfter als dreimal				

Mikrobiologische Befunde

BSI-Keim später identifiziert	Ja		Nein	
Lokalisation 1		Datum 1		
Lokalisation 2		Datum 2		
Lokalisation 3		Datum 3		
Öfter als dreimal				

Klinische Präsentation und Anamnese

Fieber		MMA		Dyspnoe	
Stenocardien		Neurologie		Tachycardie	
Diarrhoe		Verwirrung		AZ-Verschl.	
Schmerzen		Wo			
Hautveränderung		Wo			

Zuweiser

Hausarzt		Ambulanz		Anderes KH	
Dialyseinstitut		Pflegeheim		Selbst	
Sonstiges					

Aufnahme

EBA→ Station		Anderes Haus → Station		Ambulanz → Station	
EBA → ICU		Anderes Haus → ICU		Ambulanz → ICU	
NA→ ICU					
Bei HA / HCA: Onset-Station bzw. Haus					

Stationärer Verlauf

Station	von	bis	Grund der Verlegung

Stationäre Tage

	Med.	Chirurgie	Sonstige	SUMME
Normal				
Intensiv				
IMC				
SUMME				

		Begründung
Aufnahmediagnose		
Arbeitsdiagnose		
Entlassungshauptdiagnose		

Verlauf

Antimikrobielle Vortherapie innerhalb von 30 Tagen vor pos. BK[12]

Substanz und Dosis	**IV**	**PO**	**von**	**bis**	**S.**	**R**

[12] S = Sensibel; R = Resistent; A = Adäquat nach aktuellen Empfehlungen (bei MSSA: Flucloxacillin, Cefazolin…)

Antimikrobielle Therapie unmittelbar nach Abnahme der BK

Keine Änderung	

Substanz und Dosis	IV	PO	von	bis	S	R	A

Antimikrobielle Therapie nach Einlangen des Gram-Präparats

Keine Änderung	

Substanz und Dosis	IV	PO	von	bis	S	R	A

Antimikrobielle Therapie nach Antibiogramm u/o Keimnachweis

Keine Änderung	

Substanz und Dosis	IV	PO	von	bis	S	R	A

Infektiologie-Konsil vor Ort

Datum des ersten Konsils		Anzahl der Konsile	

Antimikrobielle Therapie nach Konsilen

Keine Änderung	

Substanz und Dosis	IV	PO	von	bis	S	R	A

Labor

Parameter	Letzter Vorwert	Aufnahme	BLK	Outcome
Datum				
Leukos				
Neutros %				
Hb				
Ery				
Thrombos				

Crea				
CRP				
PCT				
PZ				
D-Dimer				
AT3				
AST				
ALT				
Bili				
GGT				
Fibrinogen				

Untersuchungen

Art	Lokalisation	Datum	Vor BSI	Nach BLK Abnahme	Nach BLK pos.	Pathologie
Sono	Abdomen					
	Weichteil					
	TTE					
	TEE					
	FCDS					
CT	CCT					
	Thorax					
	Abdomen					
	Becken					
	WS					
	Extremität					
MRT	Gehirn					
	Abdomen					
	Weichteil					
	Knochen					
Szinti	Knochen					
	Leukocyten					
PET	Neo					
	Entzündung					
Röntgen	Thorax					
	Abdomen					
	Knochen					

Klinik

Tage bis Fieberfreiheit					
	Nach Aufnahme		Nach AB Einleitung		
	Nach Adaptierung[13]				
Dokumentierte klinische Besserung					
	Nach Aufnahme		Nach AB Einleitung		
	Nach Adaptierung		Konsequenz		
Dokumentierte klinische Verschlechterung					
	Nach Aufnahme		Nach AB Einleitung		
	Nach Adaptierung		Konsequenz		
Komplikationen					

	Durch Keim		Welche	
	Durch Therapie		Welche	

Outcome				
Entlassung nachhause oder normale Verlegung		Datum		Ursache
Exitus letalis		Datum		SAB related (1/0)
DNR		Datum		

Erste Wiederaufnahme		
Wegen gleicher Infektionskrankheit		
Wegen anderer Infektionskrankheit		
Wegen Therapiekomplikation		
Anderer Grund		
Keine Wiederaufnahme		

Stewardship-Parameter (für Staph aureus)

FK ex	Datum		Tage nach pos BLK		Nein	
	Welcher FK					

[13] Mit adäquatem Antibiotikum

	Begründung für Belassen											
Antibiotikum	BL 1. Wahl (1)											
	BL 2. Wahl (2)											
	BL 3. Wahl (3)											
	Non-BL (MSSA) (4)											
	Non-BL (MRSA) (5)											
	BL (MRSA) (6)											
	Sonstiges (7)											
Kombination bei FK												
Kombination bei kompl. SAB												
Therapiedauer (adäquate Thp)												
USKG	TTE		Datum		IE							
	TEE		Datum		IE							
Falls Endocarditis	AK		PK		Anmerkungen							
	MK		TK									
	Abszess		Insuffizienz									
	Leck		Vegetation									
	Sklerose		Verdickung									
	OP		Datum									
			Art									
	Bei KKE		Alles entfernt		Ja		Nein					
Kontroll-BLK	Datum		Tage nach Therapiebeginn									
	Pos		Neg									
Septische Absiedelungen	Ja		Lokalisationen	1. 2. 3.								
	Gefunden mit	1. 2. 3.										
	1. Empfehlung der Untersuchung durch Inf.Kons											
	2. Empfehlung der Untersuchung durch Inf.Kons											
	3. Empfehlung der Untersuchung durch Inf.Kons											
Ambulanzanbindung	Ja		Nein									
Konsequenzen durch Ambulanz												
Anmerkungen												

Dokumentation im AB

Diagnosen (1/0)		Labor (1/0)		Beurteilung (1/0)	