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Oral Care and the Risk of Bloodstream Infections in Mechanically

Ventilated Adults: A Review

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Summary

Rationale—Bacteremia, defined as the presence of viable bacteria in the circulating blood can result in bloodstream infection, which is one of the most frequent and challenging hospital-acquired infections. Bacteremia occurs in healthy populations with manipulation of the oral mucosa, including toothbrushing. Oral care is commonly administered to mechanically ventilated patients, and it is important to determine whether this practice contributes to the incidence of bacteremia. This paper reviews the literature on the link between the manipulation of the oral cavity and the development of bacteremia in mechanically ventilated adults.

Methods—Searches were conducted using Medline, CINAHL, and the Cochrane Library databases. Article inclusion criteria were 1) a focus on mechanical ventilation and critical illness, 2) human subjects, 3), adult subjects, and 4) publication in English (or available English translation).

Results—Nine articles met inclusion criteria and were critiqued. All relied upon clinical data as outcome measures; many were retrospective. The three organisms most often associated with nosocomial bloodstream infections were *Staphylococcus aureus*, coagulase negative staphylococci, and Enterococcus species. Establishing the origin of bacteremia was problematic in most studies.

Conclusions—Additional research is needed to understand the relationship of oral care practices to bacteremia in mechanically ventilated adults.

Keywords

Oral care; bacteremia; mechanical ventilation; bloodstream infections

Introduction

Bacteraemia, defined as the presence of viable bacteria in the circulating blood (Daly et al., 2001), can result in bloodstream infection, which is one of the most frequent and challenging hospital-acquired infections and accounts for 15% (Burke, 2003) of nosocomial infections. There is substantial evidence that bacteraemia occurs in healthy populations with manipulation of the oral mucosa, such as toothbrushing. However, there has been little examination of

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potential adverse effects of oral care in mechanically ventilated critically ill adults, and neither the relationship of oral care to bacteraemia nor the clinical significance of oral care- associated bacteraemia in these patients has been explored. Literature linking oropharyngeal colonization with the development of ventilator-associated pneumonia (VAP) (Fourrier et al., 1998; Garrouste-Org et al., 1997; Grap & Munro, 1997) has led to increased interest in the potential for oral care in the intensive care unit (ICU) to reduce the risk of VAP. With oral care becoming more commonly administered in the mechanically ventilated critically ill, it is important to determine whether this practice contributes to the incidence of bacteraemia. Mechanically ventilated critically ill patients are more susceptible to infections that can increase their length of stay, hospital costs and mortality. Because of the impact of bacteraemia on the use of healthcare resources and the potential for oral care to decrease the incidence of other systemic diseases such as VAP, it is important to know the relationship between bacteraemia and oral care in this population. Therefore, this paper will review the literature on the link between the manipulation of the oral cavity and the development of bacteraemia in mechanically ventilated adults.

Bacteraemia is one of the most frequent and challenging nosocomial infections and is a leading cause of mortality in hospitalized patients. Five to ten percent of patients in acute care hospitals acquire nosocomial infections with 25 percent of nosocomial infections occurring in ICUs (Weinstein, 1998; Jarvis, 2001). The cost of nosocomial infections is 3.4 billion pounds a year (Burke, 2003; Safdar et al., 2001). Hospital acquired bloodstream infections cause as many as 3.5 million additional hospital days per year in the US accounting for 1.7 billion pounds in additional cost (Correa & Pittet, 2000). The crude mortality rate of hospital acquired bloodstream infections is approximately 35%, with a range from 12-80% (Correa and Pittet, 2000; Wenzel & Edmond, 2001; (Pittet et al., 1994; Renaud & Brun-Buisson, 2001). Similar rates in bloodstream infections and associated mortality have been reported in European studies (Crowe et. al, 1998; Meric et al., 2005) Bloodstream infection is a leading preventable infectious complication among critically ill patients (Hugonnet et al., 2004). According to Wenzel and Edmond (2001), 49.4% of all nosocomial bloodstream infections occur in intensive care units. Bloodstream infections have been shown to increase ICU and hospital stay, increase the use of healthcare resources and significantly increase morbidity and mortality (Correa and Pittet 2000, Costa et al., 2004). Bloodstream infections in the ICU have a tremendous impact on hospital resources and costs (El-Masri et al., 2002; Pittet et al., 1994).

Search Strategy

The literature review focused on the prevalence and aetiology of bacteraemia specifically in mechanically ventilated adults. The method used in this review to outline the search strategy was based on that found in Bench (2003). Searches were conducted in Medline, Cumulative Index to Nursing and Allied Health (CINAHL), and the Cochrane Library using both MESH headings and free text words. Articles that resulted from the searches were scrutinized for the following inclusion criteria. Inclusion criteria for research articles were 1) a focus on mechanical ventilation and critical illness, 2) human subjects, 3), adult subjects included in the sample, and 4) publication in English (or available English translation). The following terms were used in the search process (*prevalence and aetiology of bacteraemia in mechanically ventilated adults*) (*prevalence of bloodstream infections in mechanical ventilation*), (*bloodstream infections and intubation*), (*bloodstream infections and critically ill*), (*bacteraemia and ICU*) (*bloodstream infections and intubation*) and (*prevalence and nosocomial bloodstream infections*).

Findings of the review

The Medline search using the phrase (*prevalence and aetiology of bacteraemia in mechanically ventilated adults*) without limits resulted in five articles; following retrieval, only one of those articles met inclusion criteria. A second search was performed using key words (*prevalence of bloodstream infections in mechanically ventilated adults*) with four articles retrieved, and one meeting inclusion criteria. A third search in Medline using key words (*prevalence and nosocomial bloodstream infections*) yielded 350 articles; 26 of these are referenced in this paper, either in the review or to support the background. The remainder articles were eliminated from inclusion in this review secondary to not meeting one of the inclusion criteria listed above. A fourth search was performed in Medline using key words (*bloodstream infections and intubation*) resulting in seventy-seven articles with two included in the review.

Three searches were conducted in the CINAHL database using keywords (*bloodstream infections and mechanical ventilation*), (*bloodstream infections and critically ill*) and (*bacteraemia and ICU*) resulting in one article that met inclusion criteria. The Cochrane Library database was searched twice using (*bloodstream infections and intubation*) and (*prevalence and nosocomial bloodstream infections*), three reviews were found, none of which were relevant to the current review. Several articles were retrieved from the reference list of articles from database searches described above. Articles with an emphasis on the outcome and impact of bacteraemia were also retrieved to support the introduction and significance of bacteraemia in mechanically ventilated subjects. A total of nine articles from all search strategies combined met the inclusion criteria and were used in the review of the prevalence, aetiology of bacteraemia in mechanically ventilated adults. The articles are included in Tables 1, 2 and 3.

Table 1 shows literature on the prevalence of bloodstream infections in mechanically ventilated critically ill adults and identifies the focal point of nosocomial bloodstream infections found in the reviewed studies (Gordon et al., 1998;Laupland et al., 2004;Renaud and Brun-Buisson, 2001;Seifert et al., 1995;Suljagic et al., 2005;Zolldann et al., 2005). The majority of the bloodstream infections were classified as primary infections (no identified source of infection). Secondary infections were further classified by the source of identical micro-organisms. Central venous catheters were the most common site of infections followed by pneumonia and urinary tract infections (Gordon et al., 1998;Renaud and Brun-Buisson, 2001;Seifert et al., 1995). There were several methodologic similarities to the reviewed studies. All were surveillance studies which relied upon clinical data for outcome measures, including microbial culture results. Retrospective reliance upon clinical cultures, rather than prospective randomized sampling, limits the identification of nosocomial infection to those instances in which clinical indications for sampling existed, and may result in under representation of bloodstream infections. All were conducted using chart review, and most were retrospective; this limited the outcome measures to those which were clinically available.

A study by Hugonnet (2004) found 554 episodes of ICU-acquired infections with primary bloodstream infections accounting for 20.4%. Three primary bloodstream infections occurred in patients without a central line, but the source of the three bloodstream infections was not identified. Exposure to mechanical ventilation was lower in subjects without bloodstream infections. The median length of stay was longer in patients with microbiologically documented (specific pathogen cultured) bloodstream infections (15.5 days) and clinical sepsis (14 days) than patients without bloodstream infections (four days) (Hugonnet et al., 2004). The occurrence of pneumonia, urinary tract infection and other infections was less frequent in patients with bloodstream infections. The study reported that illness appeared more severe in patients with clinical sepsis (39.7%) compared to those without bloodstream infections (22.7%) (Hugonnet et al., 2004). This study is important in identifying the impact of

bloodstream infections in the critically ill in regards to incidence, length of stay, mortality and concurrent illnesses as well as comparing clinical sepsis and microbiologically documented sepsis surveillance strategies. However, the researchers did not determine a definitive causative factor of the bloodstream infections nor clinical sepsis.

Another study examined the association of nosocomial bloodstream infections in critically ill adult trauma patients with injury severity scores (El-Masri et al., 2002). Injury Severity Score was a significant independent predictor of nosocomial bloodstream infections. In addition, hospital length of stay (34.8 days vs. 16.5 days) and ICU length of stay (28.1 days vs. 13 days) were significantly higher for patients with nosocomial bloodstream infections than for those without. The origin of the bloodstream infections was not examined; this is unfortunate, since identifying the origins of bloodstream infections in adult trauma patients would assist in guiding prevention methods.

Bacteraemia and Healthy Populations

There is substantial literature on the development of transient bacteraemia following manipulation of the oral mucosa in healthy populations, as well as patients at risk for cardiovascular disease. Transient bacteraemia is defined as bacteria in the bloodstream that clears within minutes by the host's reticuloendothelial system. Transient bacteraemia may be induced in virtually all healthy individuals following trauma to the mucosal surfaces of the oral cavity caused by a variety of procedures (Wank et al., 1976). Wank et al (1976) studied the frequency of bacteraemia following toothbrushing, flossing and "deplaquing" in 21 healthy subjects. The incidence of bacteraemia following manual toothbrushing ranged from 0-26% in subjects with minimal periodontal disease and the incidence was 24.2% in subjects with various degrees of periodontal disease. Another study examined the incidence of bacteraemia in patients without periodontal or gingival disease following use of an oral irrigation device, which is commonly used in the treatment and prevention of periodontal disease (Berger et al., 1974). The study found that 27% of the subjects (n=30) who used the oral irrigation device developed bacteraemia. Though healthy populations are at risk of developing transient bacteraemia from oral manipulation, this is usually of little clinical significance due to normal host defence mechanisms. Transient bacteraemia, identified by documentation of appearance of organisms in blood cultures, that clears in no more than 15-30 minutes is the most common scenario in healthy populations following translocation of micro-organisms into the bloodstream (Gendron et al., 2000; Lockhart & Durack, 1999). In healthy individuals, the micro-organisms that gain entrance to the blood and circulate throughout the body are usually eliminated by the reticuloendothelial system within minutes and lead to no clinical symptoms other than a slight increase in body temperature (Li et al., 2000). Healthy adults do not have clinical sequelae from these episodes of transient bacteraemia. However, for immunocompromised patients such as the critically ill who may have other underlying diseases and are more susceptible to bacterial colonization, transient bacteraemia could be a more significant problem. In immunocompromised individuals the disseminated micro-organisms may find favourable conditions, settle at a given site and multiply (Li et al., 2000). The duration of bacteraemia usually reflects the number and nature of the organisms as well as other host factors, bacteraemia that does not clear the immune system within minutes (such as transient bacteraemia) have the potential to affect clinical outcomes. It is not clear what role the duration of bacteraemia has on development of other systemic infections and therefore is important to explore the relationship of transient bacteraemia to the development of clinically significant bacteraemia. Because of the potential impact of bacteraemia and the vulnerability of the mechanically ventilated critically ill patient, it is important to detect specific risk factors and methods of prevention.

Toothbrushing

The American Dental Association recommends toothbrushing twice a day to prevent dental caries and disease in healthy populations. Toothbrushes are more effective in plaque removal and gingival stimulation than foam swabs and are regarded as the best tool for mechanical oral care in healthy populations (Fitch et al., 1999). However, standard recommendations of oral care for mechanically ventilated adults have not been extensively tested. In a study by Schlein et al. (1991) (n=20), the presence of bacteraemia was measured before and after toothbrushing in healthy adults. All samples were negative before the intervention but 25% of subjects had positive blood cultures following toothbrushing. Another study found that 5 of 30 patients developed bacteraemia following the use of an electric toothbrush (Sconyers et al., 1979). Another study, involving 735 children undergoing treatment for extensive dental decay, found that in 9% of children a variety of hygiene and conservative procedures, including toothbrushing, increased the prevalence of bacteraemia from 17-40% (Roberts et al., 1997). Since toothbrushing has been linked to transient bacteraemia in healthy populations, and critically ill patients may have increased vulnerability, it is important to examine transient bacteraemia from toothbrushing in the critically ill and its significance for clinical outcomes.

Increased Risk Related to Mechanical Ventilation

Bloodstream infection represents the failure of the immune system to contain infection at a focal site and the consequent occurrence of disseminated disease. Mechanically ventilated patients are more susceptible to the development of infection for many reasons. Intubation and mechanical ventilation alter the first lines of defence (Grap and Munro, 1997). Patients intubated in ICUs are at a greater risk of developing systemic diseases. The poor health status of critically ill patients and the wide use of antibiotics increase the vulnerability of these patients to nosocomial infections (Agvald-Ohman et al., 2004). Medical procedures may increase risk of infection for these patients as well. For example, Rijnders et al. (2001) looked at the incidence of bacteraemia following urgent intubation (n=68) in an adult medical ICU, and found 9% (6/68) of patients developed streptococcal bacteraemia immediately (mean 10.8 min) after urgent orotracheal intubation. This study demonstrated the development of transient bacteraemia (bacteria eliminated from the bloodstream within minutes) caused by a procedure that involves manipulation of the oral cavity in critically ill patients (Rijnders et al., 2001) and is one of few that has examined bacteraemia of oral origin in mechanically ventilated adults. Although the prevalence of bacteraemia in hospitalized patients as well as ICU patients has been described in the literature, the prevalence and oral care as an aetiology has not been examined specifically in mechanically ventilated adults.

Table 2 summarizes research studies that described the prevalence and aetiology of bloodstream infections specifically in the critically ill (Gordon et al., 1998;Hugonnet et al., 2004;Laupland et al., 2002;Laupland et al., 2004;Meric et al., 2005;Renaud and Brun-Buisson, 2001;Seifert et al., 1995;Suljagic et al., 2005;Zolldann et al., 2005). It describes the percent of patients mechanically ventilated, ICU acquired bloodstream infections along with the most common diagnosis found in the study population. In the reviewed studies, mechanical ventilation was examined in regression and univariate analysis. More than fifty percent of ICU subjects received mechanical ventilation as a therapeutic treatment in the reviewed studies. The rates of bloodstream infections in the ICU documented in multiple studies amplify the need for further investigation of prevention methods. Cardiovascular, infectious and pulmonary/respiratory are the most common diagnoses reported in studies examining bloodstream infection in critical care, probably because mechanical ventilation is a common therapeutic method implemented in the ICU for such diagnoses.

Relationship of Bacteraemia and Oral Health in Mechanically Ventilated Adults

Mechanically ventilated adults are dependent on healthcare workers to provide all aspects of their oral care. Yet, a study performed by Grap et al. (2003) assessing oral care in the ICU, found that intensive care unit nurses' mean rating of the priority of oral care was 53.9 on a 100point scale. The study data suggested that the provision of oral care to critically ill patients may be affected by the perception that oral care contributes less to the patient's health and well being (and thus is of lower priority) than other nursing interventions. Several factors, including lack of priority given to oral care, medical conditions and equipment, and inability to attend to their own care, influence the lack of a consistent oral care regimen in the mechanically ventilated adult (Munro & Grap, 2004). Nurses provide a variety of oral interventions designed to address patients' comfort, (Munro and Grap, 2004; Fitch et al., 1999; Grap et al., 2003) including toothbrushing (Grap et al., 2003; Jones et al., 2004). In surveys by Grap et al. (2003), ICU nurses reported the use of a toothbrush to provide oral care to intubated patients 38.9% of the time. However, some nurses indicated that they did not brush teeth because of perceived increase in risk of bacteraemia. Another study examined the oral care practices of critical care nurses in an adult ICU and reported that toothbrushes were used at least once a day by 85.5% of the nurses, but practices for intubated patients were not examined separately (Jones et al., 2004). Although toothbrushing is common in ICUs by nursing staff, there are no data on the relationship of toothbrushing and transient bacteraemia, no data on the significance of transient bacteraemia, and no data to indicate whether this practice increases risks of nosocomial infections.

Micro-organisms

Dental plaque provides a microhabitat for organisms and provides opportunity for adherence either to the tooth surface or to other micro-organisms (Munro and Grap, 2004; Fitch et al., 1999). The teeth are the only nonshedding surfaces in the body, and bacterial levels can reach more than 10¹¹ micro-organisms per mg of dental plaque (Li et al., 2000; Gendron et al., 2000; Wilson, 2001; Lockhart et al., 1999). Endodontal and periodontal infections are associated with approximately 200-500 species (Gendron et al., 2000). Importantly, dental plaque may serve as a reservoir in critically ill patients for potentially pathogenic microorganisms. Within 48 hours of admission to the ICU, the oropharyngeal flora of critically ill patients changes from the usual gram positive streptococci (viridans streptococci) and dental colonizers found in healthy individuals to include more potentially pathogenic microbes such as S. aureus, S. pneumoniae, A. baumanii, H. influenzae and P. aeruginosa (Munro and Grap, 2004). There have been increasing rates of bloodstream infections related to specific organisms such as S. aureus, enterococci, coagulase negative staphylococci and Candida species (Banerjee et al., 1991; Renaud and Brun-Buisson, 2001). Coagulase negative staphylococci are found among the normal flora of human skin and the mucous membranes, and are one of the most common causes of bloodstream infections (Shafazand and Weinacker, 2002; von et al., 2001) particularly in immunocompromised patients (von et al., 2001). However, because of their presence as normal flora on skin, coagulase negative staphylococci are only identified as a true cause of bloodstream infection (rather than contamination of the culture) in the presence of two positive separate blood cultures (Archer, 1985; Sheagren, 1987). Table 3 outlines the most common micro-organisms identified in positive blood cultures (Gordon et al., 1998; Hugonnet et al., 2004; Laupland et al., 2002; Laupland et al., 2004; Meric et al., 2005; Renaud and Brun-Buisson, 2001; Seifert et al., 1995; Suljagic et al., 2005; Zolldann et al., 2005). The three most common organisms found in nosocomial bloodstream infections were S.aureus, coagulase negative staphylococcus (CONS) and Enterococcus species. Grampositive organisms are becoming more frequently noted as causes of bacteraemia and CONS is becoming one of the most common organisms. Although the three most common organisms are gram-positive, both gram-negative and gram-positive organisms can cause bloodstream infections. Viridans group streptococci are most prevalent in the oral cavity and are a common

cause of endocarditis, bacteraemia and abscesses (Razonable et al., 2002; Lockhart et al., 1999). Viridans group streptococci have been shown to translocate into the bloodstream and are associated with septic shock and acute respiratory distress syndrome (Razonable et al., 2002). Tunkel & Sepkowitz (2002), reported that viridans group streptococci account for 30% of all episodes of bacteremia in hospitalized neutropenic patients Marron et al. (2000), studied the incidence and effects of viridans streptococci bacteraemia in neutropenic patients with cancer. Marron et al. (2000) found that 18% (n=485) of patients developed bloodstream infection caused by viridans streptococci. Of those patients, 11% developed serious complications such as ARDS, pulmonary infiltrates and septic shock. Oral mucositis was significantly associated with the development of complications. In an analysis of data from neutropenic patients with viridans streptococcal bacteraemia, viridans streptococci with the same ribotype as the strain responsible for bacteraemia were recovered from the mouths of all patients before the onset of bacteraemia (Tunkel and Sepkowitz 2002). This strongly suggests that the oral cavity can serve as a source of organisms responsible for bacteraemia and disruption of the oral mucosa may lead to the development of bacteraemia.

Literature supports a theoretical link between oral health and bacterial endocarditis, and transient bacteraemia associated with oral manipulations is thought to be an important cause of endocarditis (Lucas et al., 2002; Daly et al., 2001). Oral streptococci are the predominant species implicated in bacterial endocarditis and account for 40-60% of cases (Lucas et al., 2002). However, immunocompromised patients such as those who are critically ill are at greater risk of developing complications from transient bacteraemia, including the development of systemic inflammatory response syndrome (SIRS). The American Heart Association recommends that prophylactic antibiotics be administered to people at risk for cardiac conditions prior to a variety of dental procedures. These guidelines are often used by clinicians for non-cardiac conditions as well; however, there is little to no evidence for this practice because predisposing factors for other infections are not known. Knowing the incidence of transient bacteraemia related to toothbrushing in mechanically ventilated adults may provide a foundation for examining the effects of antibiotic use on the development and clinical outcomes of transient bacteraemia.

Conclusion

The high incidence of bloodstream infection and its potential impact on the development of other nosocomial infections and sequelae such as sepsis, point to the need for research to identify risk factors and methods of prevention. Much of the published research is descriptive and retrospective in design, and outcome measures of bacteraemia and its clinical consequences are not robust. Little is known about the effects of oral care interventions, specifically toothbrushing, on mechanically ventilated patients. There remains a lack of published evidence on the benefits and risks of oral care in the ICU. Well designed prospective clinical studies, with valid and reliable outcome measures, are needed. Many novel technologies for identification of micro-organisms (for example, DNA typing) are now available. These powerful methods could provide strong evidence of the origin of bacteraemia if incorporated into carefully designed clinical studies of oral care procedures in critical care units. Understanding the incidence and clinical relevance of transient bacteraemia of oral origin in the ICU is important for assessing the potential risks and benefits of oral care, for minimizing systemic processes such as sepsis, and decreasing the use of healthcare resources, length of stay and mortality.

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 Table 1

 Etiology of Nosocomial Bloodstream Infections in Critically III Adults

Other (%)	1	7.8			-	18
Surgical infection (%)		10.9				4
Pneumonia (%)		16.8	17		23.6	6
Urinary tract infection (%)		3.2	S	-	24.7	
Central venous catheter (%)	1	27.9	9	26.1		26
Secondary Infection (%)	20			45		
Primary infection (unidentified source)(%6)	55.5	33		55		
Author	Suljagic, 2004	Gordon et. al, 1998	Laupland et al., 2004	Renaud and Brun- Buisson, 2001	Zolldann et al., 2005	Seifert et al., 1995

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 Table 2

 Research Studies of Prevalence and Etiology of Bloodstream Infections in Critically III Adults
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Author	Nosocomial (%)	ICU bacteremia (%)	Non ICU bacteremia (%)	Mechanical Ventilation (%)	Design	Most prevalent diagnoses
Suljagic, 2004	55.9	34	21.7	48.9	Cohort study	Circulatory systems 25.6% Trauma and poison 20.5% Neoplasms 16.7%
Meric et. al, 2005		18.2	46.4	94.2	Prospective surveillance	Respiratory 42.3 Other 25 Infectious 17.3
Gordon et. al, 1998		23.5				Cardiothoracic patients
Laupland et al., 2004		4.4	3.8	87	cohort	
Renaud and Brun-Buisson, 2001		90.3		1	Cohort & case control	Respiratory failure 32.4 Cardiac 9.9 Central nervous system 8.1
Zolldann et al., 2005	10.7	17.2		1	Cohort	Intracranial hemorrhage 49.4% Intracranial neoplasias 25 Traumatic head 13.4
Seifert et al., 1995		l	ł	70	Cohort (retrospective)	
Hugonnet et al., 2004		20.4		67.9	Prospective surveillance	Infectious 38.7 Cardiovascular 24.2 Pulmonary 17.7
Laupland et al., 2002		22.3	1	ł	Cohort (population based)	

Microor; Author	ganisms recoven	ed from blood	cultures of crit	coag Neg	vi -	Klebsiella	Entero-		Acineto-	Fungi	۵.	н Ш
	MICTON al (%)	(%)+	(%)	Stapn (%)	Aureus (%)	spp. (%)	cuccus spp. (%)	(%)	bacter spp.(%)	(0)	Aeru ginosa (%)	iaecaus (%)
Suljagic, 2004	22	44	50	21.4	14.3	13.3	5.1	5.1	7.1	4.1		
Meric et al, 2005		-		13.3	33.3	6.7	20			13.3	6.7	
Gordon et al, 1998	5	37	41	11.4	12.4	4.2	8.9			17	10.3	
Laupland et al, 2004	22	44	21	11	18	3.6	15.5	4.9	1.6	10	4.5	20.8
Renaud & Brun- Buisson, 2001	10.8	39.6	39.6	34.1	45.5		18.2			-		
Zolldann et al, 2005				27.3	27.3		27.3	1				-
Seifert et al, 1995	35					3.0		8.8	8.1	1	7.6	1
Hugonnet et al, 2004	12	1		63.6	3			ю		3		9
Laupland et al, 2002	20	57	14	13.6	27.2		10.6	9		9	з	4.5

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