



Canadian Agency for
Drugs and Technologies
in Health

RAPID RESPONSE REPORT: SUMMARY WITH CRITICAL APPRAISAL



TITLE: Daptomycin for Methicillin-Resistant and Methicillin-Sensitive Staphylococcus Aureus Infection: A Review of Clinical Effectiveness, Cost-Effectiveness and Guidelines

DATE: 21 January 2016

CONTEXT AND POLICY ISSUES

Staphylococcus aureus is an opportunistic pathogen that can cause a variety of self-limiting to life-threatening diseases in humans. *Staphylococcus aureus* is one of the most common causes of skin, soft-tissue, and nosocomial infection.¹ Example of specific infections caused by staphylococci include cellulitis, boils, skin abscesses, surgical site infections, endocarditis, osteomyelitis and bacteremia.²

Stable beta-lactam penicillins such as cloxacillin and 1st-generation cephalosporins such as cefazolin have been the treatment of choice for staphylococci infections including methicillin susceptible staphylococcus aureus (MSSA) bacteremia.³ However, the emergence of methicillin resistant staphylococcus aureus (MRSA) complicates therapy since MRSA resists successful treatment with these antibiotics and is an independent risk factor for mortality in *staphylococcus aureus* bacteremia (SAB).³ There has been a steady increase in methicillin resistant MRSA rates across the Canada. The combined MRSA colonization and infection rate increased from 0.65 cases per 10,000 patient-days in 1995 to 12.4 cases per 10,000 patient-days in 2009, with hospital-acquires (nosocomial) MRSA accounting for nearly two-thirds of all cases (8 cases per 10,000 patient-days in 2009).⁴ National prevalence estimates for MRSA, vancomycin-resistant *Enterococcus* (VRE) and *C. difficile* infection (CDI) in Canadian hospitals published in 2013 found that the median (range) prevalence rates for MRSA colonization or infection was 4.2% (0% to 22.1%), although for MRSA infection alone the median rate was 0.3% (0% to 5.9%).²

Increasing attention has been focused on the severity and frequency of infections caused by MRSA, since it has been associated with higher rates of morbidity and mortality, prolonged hospital stay, and substantial higher healthcare costs compared to MSSA.^{2,4}

Intravenous vancomycin is the treatment of choice for MRSA bacteremia and other deep infections including endocarditis, peritonitis, necrotizing pneumonia, meningitis, osteomyelitis, septic arthritis, and infections of bones, joints and organs.¹ Clinical isolates of MRSA that

Disclaimer: The Rapid Response Service is an information service for those involved in planning and providing health care in Canada. Rapid responses are based on a limited literature search and are not comprehensive, systematic reviews. The intent is to provide a list of sources of the best evidence on the topic that CADTH could identify using all reasonable efforts within the time allowed. Rapid responses should be considered along with other types of information and health care considerations. The information included in this response is not intended to replace professional medical advice, nor should it be construed as a recommendation for or against the use of a particular health technology. Readers are also cautioned that a lack of good quality evidence does not necessarily mean a lack of effectiveness particularly in the case of new and emerging health technologies, for which little information can be found, but which may in future prove to be effective. While CADTH has taken care in the preparation of the report to ensure that its contents are accurate, complete and up to date, CADTH does not make any guarantee to that effect. CADTH is not liable for any loss or damages resulting from use of the information in the report.

Copyright: This report contains CADTH copyright material and may contain material in which a third party owns copyright. **This report may be used for the purposes of research or private study only.** It may not be copied, posted on a web site, redistributed by email or stored on an electronic system without the prior written permission of CADTH or applicable copyright owner.

Links: This report may contain links to other information available on the websites of third parties on the Internet. CADTH does not have control over the content of such sites. Use of third party sites is governed by the owners' own terms and conditions.

require a higher minimum inhibition concentration (MIC) of vancomycin (but still susceptible) have emerged, raising concerns among clinicians because all-cause mortality among patients with MRSA bacteremia caused by isolates with higher vancomycin MIC is significantly higher than among patients infected with lower vancomycin MIC isolates.³

Newer alternative antibiotics that are active against MRSA, including isolates with higher MIC of vancomycin, offer options for the successful management of staphylococci infections. Relative resource utilization with antibiotic therapy such as length of hospital stay, the need for adjunctive procedures, and monitoring the serum levels of antibiotics may differ with different antimicrobial agents; and it is important to understand these differences since the potential economic benefits can be influenced by the treatment decisions.^{5,6}

Daptomycin is lipopeptide antibacterial agent administered once daily, which has a rapid bactericidal activity against Gram-positive bacteria.⁷ The drug works by binding to the cell membrane of susceptible organisms and inhibiting protein synthesis by disrupting the membrane electrical potential, which leads to bacterial death. Unlike vancomycin which has not proven effective to treat bacteremia caused by MSSA, daptomycin has been found to be similarly efficacious as cloxacillin and vancomycin for the treatment of bacteremia caused by MSSA and MRSA, respectively.⁸

The aim of this review is to summarize evidence on the comparative clinical and cost effectiveness of daptomycin to other antibiotics for the treatment of bacteremia and other infections caused by MSSA or MRSA, and to summarize evidence-based guidelines regarding the use of daptomycin for MRSA and MSSA bacteremia or infection.

RESEARCH QUESTIONS

1. What is the comparative clinical effectiveness of daptomycin versus alternative antibiotic therapies for MRSA and MSSA bacteremia or infection?
2. What is the cost-effectiveness of daptomycin versus alternative antibiotic therapies for MRSA and MSSA bacteremia or infection?
3. What are the evidence-based guidelines regarding the optimal dose of daptomycin for MRSA and MSSA bacteremia or infection?
4. What are the evidence-based guidelines regarding the use of daptomycin for MRSA and MSSA bacteremia or infection?

KEY FINDINGS

There was no significant difference in clinical outcomes between daptomycin, linezolid and vancomycin for the treatment bacteremia, skin and soft tissue infections (SSTI), and complicated skin and skin structure infections (cSSSI) caused by *Staphylococcus aureus* including MRSA. There was no significant difference between daptomycin, linezolid and vancomycin with regards to infection related length of stay (IRLOS) in hospital, total length of stay, medical resource utilization, and clinical response measures such as cure, improvement, no improvement, or failure. The efficacy of daptomycin was also comparable to vancomycin as supplemental prophylaxis to reduce the incidence of surgical site infections caused Gram-positive pathogens, including MRSA. Overall, the efficacy of daptomycin for the treatment of bacteremia or other infections caused by MRSA was comparable to other MRSA-active, and MSSA-active antibiotics.

The total cost of therapy for MRSA and MSSA bacteremia and other infections was mainly driven by costs associated with hospitalization instead of drug acquisition costs. There was no conclusive evidence of superior overall cost-effectiveness of daptomycin over other antibiotics, or vis-versa.

The literature search for this review did not find any studies which investigated the optimal dose of daptomycin for the treatment of MRSA and MSSA bacteremia or infection. In general, vancomycin seems to be the recommended first choice of therapy for MRSA (not MSSA) bacteremia and infections. However, in cases involving MSSA or where clinical isolates have higher vancomycin MIC or vancomycin treatment failure, daptomycin is a preferred treatment option.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic studies, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and December 15, 2015.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult patients in acute care with Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA) and Methicillin-Sensitive <i>Staphylococcus Aureus</i> (MSSA) attributed bacteremia, or infection including: <ul style="list-style-type: none"> • Skin and soft tissue infection (SSTI) • Prosthetic joint infection • Osteomyelitis • Septic joint infection • Intraabdominal infection
Intervention	Daptomycin (Cubicin)
Comparator	<ul style="list-style-type: none"> • For research questions 1 and 2: Any alternative antibiotic therapy (e.g., cloxacillin, vancomycin, linezolid) • For research questions 3 and 4: No comparator
Outcomes	<ul style="list-style-type: none"> • For research question 1: <ul style="list-style-type: none"> ○ Clinical effectiveness; including length of hospital or ICU stay, all-cause and infection-related mortality, rate of infection, quality of life, duration of treatment, rate of relapse and patient compliance ○ Harms; including adverse events such as nausea vomiting, and toxicity; rate of complications such as renal impairment, neuropathy, eosinophilic pneumonia, rhabdomyolysis; and adverse drug interactions • For research question 2: <ul style="list-style-type: none"> ○ Cost-effectiveness outcomes • For research questions 3: <ul style="list-style-type: none"> ○ Evidence-based clinical guidelines regarding the optimal dose of daptomycin • For research questions 4: <ul style="list-style-type: none"> ○ Evidence-based clinical guidelines regarding the choice of antibiotic therapy for MRSA infections including bacteremia
Study Designs	HTA/systematic reviews/meta-analyses; randomized controlled trials; economic evaluations; and evidence-based clinical guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, or were published prior to 2010. Review articles, editorials, guidelines/consensus statements without evidentiary support, and studies reporting duplicate data or subgroup analyses of already selected published studies were excluded.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using the AMSTAR⁹ checklist, randomized controlled trials (RCTs) were critically appraised using the Downs and Black checklist for measuring quality of studies,¹⁰ economic studies were assessed using the

Drummond checklist,¹¹ and clinical practice guidelines were assessed with the AGREE II instrument.¹² Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study was described narratively. The strengths and limitations of the individual studies are summarized in Appendix 3.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 464 citations were identified in the literature search. Following screening of titles and abstracts, 424 citations were excluded and 40 potentially relevant reports from the electronic search were retrieved for full-text review. The grey literature search did not find potentially relevant publications. Of these potentially relevant articles, 29 publications were excluded for various reasons, while 11 publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Additional references of potential interest that did not meet the selection criteria are provided in Appendix 5.

Summary of Study Characteristics

Study Design

Three systematic reviews,^{3,6,13} three RCTs,^{5,7,14} two economic evaluations,^{15,16} and three clinical practice guidelines^{8,17,18} met the inclusion criteria for this review. One systematic review with a network meta-analysis (NMA)¹³ was published in 2015 and included 35 RCTs published between 2000 and 2014. The NMA compared the efficacy and safety of multiple antimicrobial agents (including daptomycin) for the treatment of acute bacterial skin and skin structure infections (ABSSSI). A systematic review of 21 meta-analyses⁶ was published in 2015. The included meta-analyses evaluated the clinical efficacy and safety of MRSA-active antibiotics and were published from 2008 to 2014. One systematic review³ was published in 2014 and sought to answer two research questions, one of which was of interest to this review since it investigated evidence for the optimal antibiotic therapy for MRSA bacteremia. The investigators performed separate systematic literature searches to answer each of the two research question. Eighty-one primary studies were found for the question on optimal antibiotic therapy for MRSA bacteremia, following a search of the relevant databases for studies published from 1990 to 2014.

All the RCTs^{5,7,14} selected for this review were published in 2015. Two RCTs^{5,7} were prospective open-label studies and the other was a prospective double-blinded study.¹⁴ One RCT was a multi-center study conducted at 36 sites (including academic and nonacademic)⁵ while the other RCTs were single-setting studies conducted in the emergency department-based observational unit⁷ and the department of surgery¹⁴ of university hospitals. The multi-center RCT⁵ was described as a pragmatic study, with flexible conditions intended to reflect as much real-world practice as possible. Therefore, no specific site characteristics, investigator criteria, or prior experience with the alternative interventions being compared were necessary, and the treatments were administered in accordance with the local practice. One single-center RCT⁷ was a non-inferiority trial.

One systematic review of pharmacoeconomic studies¹⁵ was published in 2012, and included 15 pharmacoeconomic studies based on active-controlled RCTs (n=2), national claims databases (n=2), an independent prospective study, decision analytic models (n=5), and abstracts (n=5) in which decision analytic models were used to determine the cost-effectiveness of alternative interventions. The included primary studies were published from 2001 to 2011. The other economic study¹⁶ was based on a retrospective study of records from a single hospital for the treatment of complicated skin and skin structure infections (cSSSI) from February to June 2007.

The included clinical practice guidelines were published in 2015,⁸ 2014¹⁷ and 2011¹⁸. Evidence for the recommendations in each of the guidelines was based on literature from systematic searches of relevant databases, combined with opinions of experts in field.^{8,17,18}

Country of Origin

One systematic review¹³ was authored by investigators from The United Kingdom (UK) and the United States of America (USA). Another systematic review⁶ was performed by authors from Greece and UK, while a third systematic review³ was performed by authors from the USA. The primary studies included in the systematic reviews^{3,6,13} originated from multiple countries. The systematic review of pharmacoeconomic studies¹⁵ was performed by authors from the USA and included primary studies from multiple countries. One economic study¹⁶ was authored in the USA, based on a retrospective study of hospital records. One clinical practice guideline⁸ was developed in Spain while two guidelines^{17,18} were developed in the USA.

Patient Population

The primary studies in one systematic review¹³ included adult patients with ABSSSI. ABSSSI was defined as bacterial infections of the skin with a lesion size of at least 75 cm² (measured by the area of redness, edema, or induration) and includes cellulitis, wound infection, and abscesses with surrounding cellulitis.¹³ The overall reported mean age across studies varied from 36.2 to 76.0 years. The review of meta-analyses⁶ included studies in which patients were treated for Gram-positive skin and soft tissue infections (SSTI) including cases caused by MRSA. Further details about patients' characteristics were not provided. Another systematic review³ included studies involving patients who had been diagnosed with *Staphylococcus aureus* bacteremia (SAB). The mean age across studies that evaluated daptomycin ranged from 50.5 to 67.2 years across treatment arms.

One RCT⁵ included 250 adult patients (≥18 years) hospitalized for cSSSI caused by suspected or documented MRSA infection requiring inpatient treatment with intravenous (IV) antibiotics for 3 to 14 days. Additional study eligibility requirements included at least three of the following clinical signs and symptoms associated with cSSSI: pain and tenderness with palpation, elevated temperature (>37.5 °C oral or >38 °C rectal); elevated white blood cell count (>10 × 10⁹/L); swelling and/or induration or erythema; or purulent or seropurulent drainage or discharge. One RCT⁷ involved 100 patients with mean age was 40 ± 13 years who had been diagnosed with cSSSI and admitted to an observational unit in a hospital emergency department. Another RCT¹⁴ randomized 200 adult patients (≥ 18 years of age) undergoing a groin or lower extremity surgery or elective arterial revascularization.

The systematic review of pharmacoeconomic studies,¹⁵ involved patients treated for complicated skin and soft tissue infections (cSSTI) or cSSSI. Eighteen of the 21 included studies had a total of 16,459 patients. Sample sizes were not reported for the remaining five

primary studies. The reported mean age across the primary studies varied from 46.3 to 77.0 years old. The other economic evaluation¹⁶ was based on data from 82 adult patients hospitalized with cSSSI due to suspected or documented MRSA. The mean age was 54 years in one treatment arm and 60 years in the other treatment arm.

Two of the clinical practice guidelines^{17,18} had recommendation statements for children and adults, while the other guideline⁸ did not have any age specification. For this review, the discussion of guideline recommendations will be limited to adult patients, where applicable.

Interventions and Comparators

One systematic review¹³ included primary studies that investigated several interventions including ceftaroline, dalbavancin, daptomycin, linezolid, oritavancin, teicoplanin, tigecycline, and vancomycin. Of the 35 primary studies included in the NMA, only two RCTs (n = 105) involved daptomycin as treatment, with the key pathogens identified as MRSA in one RCT and broadly as *Staphylococcus aureus* in the other RCT. In the review of meta-analysis,⁶ the included studies compared daptomycin to anti-staphylococcal penicillins and glycopeptides (mainly vancomycin). Daptomycin was administered at a dose of 4 mg/kg/day for 7 to 14 days in most studies. One its primary meta-analyses evaluated administered daptomycin at a dose of 10 mg/kg/day for 4 days. Vancomycin was dosed at the standard dosage of 1 g IV every 12 hours. In one systematic review,³ daptomycin, at a dose ranging from 6mg/kg/day to 10mg/kg/day, was compared with vancomycin as part of standard therapy for patients diagnosed with SAB, with or without endocarditis. The exact dose of vancomycin was not specified.

The three selected RCTS^{5,7,14} for this review compared daptomycin (4mg/kg once daily) to vancomycin. In one RCT⁵ vancomycin was dosed at the investigators discretion according to institutional practice, while in another RCT⁷ vancomycin was administered at a dose of 15 mg/kg at baseline and repeated at 12 hours for a maximum of 2 doses. In one RCT,¹⁴ both daptomycin and vancomycin were administered in addition to background cefazolin. The dose of vancomycin was not specified.

In the systematic review of pharmacoeconomic studies,¹⁵ daptomycin, linezolid, tigecycline, and vancomycin were the main alternative interventions that were evaluated. Doses of the alternative interventions were not provided. Another economic study¹⁶ compared daptomycin, linezolid and vancomycin. Cost studies were based on overall average daily quantity of each intervention (576mg, 1200mg and 2430 mg, respectively), without specifying the actual dose per patient's body weight.

The clinical practice guidelines^{8,17,18} discussed many antibiotic therapy options for different infections. To answer the specific questions of this review, discussions of recommendations from the guidelines are limited to daptomycin for MRSA or MSSA infections.

Outcomes

The outcome measures in one systematic review¹³ included clinical response, clinical cure, early clinical response, lesion size reduction, relapse or recurrence, sustained clinical response, and incidence of adverse events (AEs). The review of meta-analyses⁶ broadly categorized outcome measures as clinical and microbiological efficacy outcomes, and treatment related-adverse events (e.g., elevation in creatine phosphokinase, nausea, headache, and renal AEs). The efficacy outcomes were not defined. Outcome measures in another systematic review³

included clinical success (cure, or improvement), clinical failure (mortality, persistent bacteremia ≥ 7 days, or recurrence within 30 days) microbiological success, duration of antibiotic therapy, duration of SAB, length of stay in hospital and AEs.

The primary outcome measure of one RCT⁵ was infection-related length of stay (IRLOS), defined as the number of hours of hospitalization associated with cSSSI management, beginning at study drug initiation and ending at discontinuation of all antibiotic therapy for cSSSI or therapy for antibiotic-related adverse events or at hospital discharge, whichever occurred first.⁵ Secondary end points included health care resource utilization, total length of stay (LOS), cost, clinical response, and patient-reported outcomes.⁵ Patient-reported outcomes were pain, infection status as measured by the Patient Global Impression of Improvement (PGI-I) scale, and quality of life (as rated by the EuroQol 5 Dimensions multi-attribute questionnaire). Patient-reported outcomes of pain and quality of life were assessed as changes from baseline using last observation carried forward methodology.

In another RCT,⁷ the primary endpoint was meeting a pre-specified objective discharge criteria with no change in antibiotic therapy or return to the emergency department for the same cellulitis within 30 days of discharge from the observational unit. Observation unit discharge criteria were defined as stable vital signs, stable or improving clinical signs and symptoms, cellulitic lesion remaining within baseline margins (a $< 10\%$ increase from baseline), an increase of no greater than 1 inch on the pain scale, and the ability to tolerate medications, fluids, or food orally.⁷ A decrease in the antibiotic dose or change from IV to oral regimen for patients was not considered a change in therapy.

In one RCT¹⁴ the outcome measure was surgical site infections defined as infections by either cellulitis adjacent to a recent surgical site or purulent discharge from a surgical site. The infections were classified, based on time to onset after the vascular procedure, as early- (occurring within 30 days), intermediate- (30 to 90 days), and late- infections (> 90 days).

The outcome measure of the economic studies^{15,16} were direct treatment costs using the payer's (health care systems') perspective. While one study¹⁵ did not report any itemization of the total cost, another study¹⁸ reported drug acquisition costs, hospital ward costs, and intensive care unit (ICU) costs that constituted the total costs.

Summary of Critical Appraisal

The three systematic reviews,^{3,6,13} were based on a comprehensive search of relevant databases. One systematic review,³ augmented the searches by reviews of the bibliographic references from the included studies. In all the three systematic reviews,^{3,6,13} the objectives and inclusion and exclusion criteria were well-described, and the list of included studies were provided in tabular form with summary characteristics. In one study³ included studies were selected and graded independently by two reviewers, with differences resolved by consensus, or through a resolution review by a third author. Two systematic reviews^{6,13} did not provide adequate information about the selection procedure of the included studies. Two systematic reviews^{3,13} evaluated the quality of their included studies and linked their conclusions with the strengths of the assessed evidence. One study⁶ did not evaluate the quality of its included studies, and reported data without applying any evidence synthesis methods. Two of the systematic reviews^{3,13} were not industry funded while one⁶ was funded by a pharmaceutical company.

The three RCTs^{5,7,14} had clearly defined objectives. They all reported the characteristics of the included study population, and in each study, baseline patient characteristics were generally similar across study arms. Two RCTs^{5,7} clearly defined the intervention of interest including doses, while one¹⁴ only mentioned the treatments by name without doses. The main outcomes were well-defined in all the RCTs^{5,7,14} and each study clearly described their respective main findings. While one study was a double-blind RCT,¹⁴ two RCTs^{5,7} were open-label studies. All the RCTs^{5,7,14} performed sample size calculations to ensure sufficient power to detect relevant differences between their respective treatment groups. One study⁵ based its primary analysis on all randomized patients and there was no report of missing data. One RCT⁷ reported that 20% of patients were lost to follow-up. The characteristics of these patients lost to follow-up were inadequately reported, although the number was similar across treatment groups, and the patients who were lost to follow-up were considered treatment failure, suggesting that the reported outcomes may be conservative. In one RCT¹⁴ the analysis was based on a modified population size, 10% lower than the randomized population due to dropouts. Missing data was not accounted for and the distribution of dropouts across study arms was not well reported. Therefore, the potential for the study to be underpowered and the possibility of bias due to missing data cannot be ruled out. All the RCTs^{5,7,14} were conducted in the USA; therefore, the generalizability of their findings to Canada is unknown, especially since microbial susceptibility to antibiotics can vary across geographical locations.

Both of the economic studies^{15,16} selected for this review had well-defined objectives, with clearly stated or implied perspective for their respective analyses. The alternative interventions under evaluation were also clearly stated in each study^{15,16}. The authors of each study^{15,16} declared no financial involvement with any organization that could be a source of potential conflict of interest with their respective studies. However, in one study¹⁵ a researcher had received grants from pharmaceuticals companies, while another was on the speaker's panel for some pharmaceutical companies. In the other study,¹⁶ one of the two authors served on the speaker's bureau for a pharmaceutical company. Both studies^{15,16} adopted the payers' perspective of the economic analysis, which does not take into account indirect costs, patient out-of-pocket costs or quality-adjusted life years. Therefore, the actual total costs of the interventions are unknown.

One economic evaluation¹⁵ was based on a systematic review of 15 pharmacoeconomic studies from multiple countries selected after a comprehensive literature search. In addition, inputs for the cost estimates of this study¹⁵ were sourced from peer-reviewed published literature or national databases, thereby increasing their likelihood of being credible. Thus the potential for the generalizability of the findings from this study to other settings was enhanced. However, details about the primary studies which furnished data for the economic evaluations were not well reported. Therefore, it was difficult to assess whether the study protocols including the doses of the alternative drugs that were administered and the general quality of care across study groups were fairly compared in accordance with regular practice without significant potential for biases. Furthermore, only the total direct costs for treatment, based on historical values of estimates for each intervention were given. Thus, it was difficult to assess whether the included cost items were appropriate, and to ascertain the generalizability of the study finding to the current Canadian context.

Another economic evaluation¹⁸ based the analysis on actual hospital records, thereby eliminating potential for errors (underestimation or over-estimations) that may be associated with literature sources and projections. The study¹⁸ also provided some itemized costs alongside the total costs of therapy to facilitate the assessment of the contributions of the

various aspects of the therapies. However, with data from a single hospital in the USA, and given that the analysis was based on historical costs without discounting for the future, the generalizability of the study findings to the Canadian context is unknown.

The development of all the three clinical practice guidelines^{8,17,18} was sanctioned by respectable professional associations (Infectious Diseases Society of America [IDSA]^{17,18} and the Spanish Society of Clinical Microbiology and Infectious Diseases [SEIMC]⁸). Each guideline^{8,17,18} had clearly described objectives, targeted users and population to whom the recommendations were meant to apply. The recommendations from each guideline^{8,17,18} were reached by consensus among experts based on evidence obtained from systematic critical review of literature, and where necessary on opinions of experts. The strength of each recommendation was rated based on the quality of evidentiary support. Before the guidelines were published, members of the respective associations were given the opportunity to appraise the recommendations.^{8,17,18} The final guidelines had the approval of the governing executives of the various professional bodies.^{8,17,18} Two of the guidelines^{17,18} were endorsed by independent external professional bodies. There was no evidence that the other guideline⁸ was externally reviewed and endorsed. However, considering the specialized nature of the professional association which commissioned the development and vetted the recommendations, it is unlikely that a superior review could have been done by external experts.

Some quality measures such as criteria for selection of evidence, procedure for updating the guideline, which are determinants of the rigor of processes and procedures for the development of the guideline, were not available for assessment. In addition, there was no indication that any of the guideline developing panels sought the input of the target population (patients, the general public). Furthermore, each member of the various panels of experts who prepared the guidelines^{8,17,18} had either received academic grants, and/or been a consultant or speaker for some pharmaceutical company. All the guidelines^{8,17,18} were developed outside Canada. Therefore, considering that microbial susceptibility to antibiotic therapy can vary from one geographical region to another, even within one country, the generalizability of the recommendations of the guidelines in Canada is uncertain.

Summary of Findings

What is the comparative clinical effectiveness of daptomycin versus alternative antibiotic therapies for MRSA and MSSA bacteremia or infection?

One systematic review¹³ which assessed test-of-cure found that there was no significant difference between the daptomycin and vancomycin in a sub group of patients with acute bacteria skin and skin structure infections (ABSSSI) caused by MRSA. The mean odds ratio (OR) with 95% credible interval for the comparison was 0.74 (0.13, 3.66). A NMA of several antibiotics, including daptomycin, found that oritavancin 1200 mg and linezolid were also equivalent to vancomycin with OR (95% CrI) of 1.06 (0.80, 1.43) and 1.55 (0.91, 2.57), respectively; thus suggesting that daptomycin may be equivalent to these antimicrobials of ABSSSI.

One review of meta-analyses⁶ found no statistically significant differences between daptomycin and anti-staphylococcal penicillins or vancomycin with regards to successful treatment of skin and soft tissue infections (SSTIs) and complicated skin and soft tissue infections (cSSTIs) caused by MRSA. The study⁶ reported evidence for shorter treatment duration with daptomycin

than comparators, with 63% of patients requiring less than a week's treatment with daptomycin versus 33% of patients in the comparator group.

In a systematic review³ to find evidence for the optimal antibiotic therapy for MRSA infections, one high-quality primary open-label RCT reported that daptomycin was non-inferior to a combined low-dose, short course gentamicin plus either an anti-staphylococcal penicillin for MSSA bacteremia (absolute difference 2.4% with 95% confidence interval [CI]: -10.2, 15). The authors concluded that daptomycin was also non-inferior to vancomycin for MRSA bacteremia with an absolute difference (95% CI) of 12.6% (-7.4, 32.6). The difference was not statistically significant ($P = 0.28$), however, the non-inferiority margin was not reported. The quality of the other primary studies of this systematic review³ were graded as low or very low and their outcomes showed no significant differences between the alternative interventions.

One RCT⁵ found no difference between daptomycin and vancomycin treatment groups with regards to intervention-related length of stay (IRLOS) and total length of stay (LOS). However, a multivariate analyses demonstrated that vancomycin treatment had a lower likelihood of achieving clinical success within 2 days (OR = 0.498, 95 % CI: 0.25, 1.0 $P < 0.05$). However, more than 80 % of patients in both treatment groups achieved clinical success by day 3, and the average LOS was approximately 4 days in each treatment group, regardless of whether patients achieved clinical success by day 2 or day 3. There were no differences between groups in patient-reported outcomes of pain, health-related quality of life, or infection status.

One RCT⁷ reported that daptomycin is non-inferior to vancomycin for the treatment of cSSSI in the observation unit of an emergency department. Fifty-four percent (54%) of daptomycin-treated patients met the primary endpoint compared with 48% of vancomycin-treated patients. Furthermore, 35 treatment failures occurred in the daptomycin group compared with 36 in the vancomycin group. The relative risk (RR) (95% CI) was 1.13 (0.77, 1.65). The RR margin of non-inferiority was set to 1.3 but there was no the evidence to support the choice of this margin⁷

In one RCT,¹⁴ 14% of patients in the cefazolin plus daptomycin treatment arm developed a surgical site infection compared with 9% of patient in the cefazolin plus vancomycin arm. Evaluation of MRSA infections found a single incidence (1.08%) of MRSA infections in the cefazolin/daptomycin group within 90 days of surgery and no occurrence of MRSA infections in the cefazolin/vancomycin group. Incidence of readmissions related to surgical site infections occurred in 11.8% of patients in the daptomycin group and 4.71% of patients in the vancomycin group. The difference was not statistically significant ($P = 0.11$). Overall, there was no demonstrated advantage for one combination regimen over the other.

One review of meta-analyses⁶ found that the safety of daptomycin in all infections was comparable with controls for all-cause mortality and total treatment-related AEs, although serious adverse events were less with daptomycin. The OR (95% CI) for treatment-related adverse events of daptomycin versus comparators was 1.06 (0.71, 1.59). The difference was not statistically significant. However, patients treated with daptomycin were more likely to have elevation of creatine phosphokinase levels compared to comparators (OR = 1.95, 95% CI: 1.04, 3.65). In most cases, the condition was reversible during or after treatment.⁶ Daptomycin was associated with a lower incidence of renal AEs, nausea and headache than comparators. Treatment discontinuations or mortality were also similar for all interventions with no significant difference in trend observed (OR = 0.71, 95% CI: 0.46, 1.10). One RCT⁷ reported four (8%) adverse events in the daptomycin group compared with seven (14%) in the vancomycin group. There were no serious adverse events reported.

What is the cost-effectiveness of daptomycin versus alternative antibiotic therapies for MRSA and MSSA bacteremia or infection?

A systematic review of pharmacoeconomic studies¹⁵ reported that in one of its primary studies from the USA, the treatment of MRSA cSSTI daptomycin was associated with higher total direct costs of treatment (US\$11,362) compared with linezolid (US\$8149), vancomycin (US\$8974), and tigecycline (US\$10,333). Another primary study from the USA in this systematic review¹⁵ found that linezolid was dominant compared to daptomycin for the treatment of suspected or confirmed MRSA cSSTI. However, in a sensitivity analyses where LOS of patient treated with daptomycin was changed from 6.8 to 4 days, the incremental cost-effectiveness ratio (ICER) for linezolid compared with daptomycin was US\$182,789 per additional successful cure gained. The dominance of linezolid was attributed to its oral formulation that is equivalent to the parenteral formulation, and thus afforded early discharge from hospital and conferred cost savings. However, from the same systematic review¹⁵ an included primary study from Mexico reported cost-effectiveness ratio for daptomycin of US\$52,135.67 per success compared with US\$67,623.14 for linezolid.

The cost analysis from one RCT⁵ found that the mean total inpatient cost for the treatment of cSSSI caused by suspected or documented MRSA was higher (\$9641) with daptomycin than with vancomycin (\$9083). The drug cost for daptomycin was significantly greater than that of vancomycin. However, daptomycin was associated with significantly lower laboratory and radiologic test costs than vancomycin ($P < 0.001$ for both comparisons). Length of stay (LOS) in the hospital was the primary driver of cost in both treatment arms, contributing 85.9 % to the total hospitalization cost, compared with 6.4 % for drug costs.

Another cost analysis based on a retrospective study¹⁶ found that the mean total cost of therapy per patient using daptomycin (\$5364.48) was higher than therapy with vancomycin (\$4703.57) but lower compared with linezolid (\$6384.79). The drug acquisition and administration costs were lowest for vancomycin (\$123.78) compared with daptomycin (\$1017.17) and linezolid (\$872.29). The main drivers of the mean total cost were hospital ward costs (\$3904.04, \$2749.19, and \$3192.57, for vancomycin, daptomycin, and linezolid, respectively), and ICU costs (\$675.75, \$1598.12, and \$2319.93, respectively).

What are the evidence-based guidelines regarding the optimal dose of daptomycin for MRSA and MSSA bacteremia or infection?

The literature search for this review did not find any studies which investigated the optimal dose of daptomycin for the treatment of MRSA and MSSA bacteremia or infection.

What are the evidence-based guidelines regarding the use of daptomycin for MRSA and MSSA bacteremia or infection?

Bacteremia

One guideline⁸ recommended daptomycin at a dose of 10mg/kg/day as the treatment of choice for complicated bacteremia caused by MRSA (A-III). Furthermore, the guideline recommended that for suspected MRSA bacteremia, a high-dose daptomycin (>10mg/kg/day) alone is an alternative empirical treatment in place of a combination therapy of a penicillinase-stable beta-lactam plus a second bactericidal antibiotic with activity against MRSA.(A-II) Another guideline¹⁸ recommended daptomycin at a dose of 6 mg/kg/daily for at least two weeks as a treatment option for uncomplicated bacteremia, extending treatment duration to at least four to six weeks

for complicated bacteremia (A-I). One guideline⁸ stated that daptomycin alone may also be used as alternative treatment to vancomycin for catheter-related bacteremia caused by MRSA (A-I), and daptomycin in combination with cloxacillin was recommended as treatment option for complicated bacteremia caused by MSSA (A-III). One guideline¹⁸ recommended that where the microbial isolate is susceptible, high-dose daptomycin (10 mg/kg/day) in combination with another agent (e.g. gentamicin 1 mg/kg IV every 8 hours) should be considered for the management of persistent MRSA bacteremia and vancomycin treatment failures (B-III).

Other infections

One guideline⁸ stated that daptomycin (>10mg/kg/day) in combination with cloxacillin is the treatment of choice for nosocomial or health-care related infective endocarditis (IE). Daptomycin was also the recommended treatment for native valve IE caused by MRSA with vancomycin MIC \geq 1.5mg/L.(B-II). However, another guideline¹⁸ recommended daptomycin at a lower dose of 6 mg/kg/daily for 6 weeks as treatment option for IE, adding that some experts recommend higher dosage of 8 to 10 mg/kg daily. (B-III)

One guideline¹⁷ recommended daptomycin (4mg/kg/day) as a treatment option for skin and soft tissue infections (SSTI) or surgical site infections where risk factors for MRSA such as nasal colonization, prior MRSA infection, recent hospitalization, and recent antibiotics are high. (Strong, low). Another guideline¹⁸ stated that treatment with daptomycin (4mg/kg/day) is a recommended empirical option for hospitalized patients with cSSTI (A-1); and daptomycin (6mg/kg/day) is a recommended treatment option for bone and joint infections such as osteomyelitis or septic arthritis. (B-II)

Limitations

For all the systematic reviews^{3,6,13} which assessed clinical outcomes, there was a limited number of primary studies that evaluated the comparative effectiveness of daptomycin. In a systematic review¹³ of 52 trials, only two of the 35 studies included in a meta-analysis had daptomycin as treatment. The review of meta-analyses⁶ included 21 studies of which three had daptomycin as treatment. One systematic review³ evaluated 81 primary studies to find an optimum antibiotic therapy for MRSA. However, its conclusions were based on one open-label RCT since the quality of the rest of the studies was rated as low or very low. In each study, daptomycin was compared directly with only vancomycin. Although two systematic reviews^{6,13} performed indirect comparisons using NMA, there was no head-to-head comparison between daptomycin and any of the newer antibiotics for MRSA or MSSA infections of any kind. Therefore, taken together, it is difficult to draw a strong conclusion about how the clinical effectiveness of daptomycin compares with that of these other drugs from the systematic reviews.^{3,6,13}

One RCT⁵ sought to mimic regular practice as much as possible. Therefore, the study protocol set only the first study drug dose, with the remaining doses, as well as all subsequent care decisions left to the discretion of the treating physician. Thus, based on the local hospital practice, the physicians decided the length of therapy, when to discontinue treatment, and whether to convert from IV therapy to oral therapy. No restrictions were imposed regarding concomitant medications, adjunctive procedures, or other therapy.⁵ The level of flexibility and lack of standardization in this RCT⁵ was likely to introduce imbalances that could bias the findings of the study. Another source of potential bias was that because cultures were not

obtained for all patients, the prevalence of MSSA across the study arms was not assessed. Imbalance in MSSA across treatment arms could introduce bias since daptomycin is known to be more active against MSSA while vancomycin is not recommended for the treatment of MSSA infections due to associated increased risk for treatment failure compared with other antibiotics. Although the criteria for meeting the endpoint in one RCT⁷ required no change in antibiotic therapy or return to the emergency department for the same cellulitis within 30 days of discharge from the observational unit, no mechanism was put in place to control or monitor outpatient compliance with the prescribed oral antibiotics. Thus, one is unable to determine if there were occurrences, including compliance issues, which could bias the study findings while the patients were on their own. Moreover, although the efficacy analysis of this study⁷ was based on the intention-to-treat population, all the patients lost to follow-up were considered treatment failures, which may not reflect the true response to the interventions. In addition, it is unknown how the margin of non-inferiority was determined.

In one RCT,¹⁴ patients who were lost to follow-up were not accounted for in the efficacy analysis which was based on the number of patients (n=178) for whom data was available. In addition, because the number of randomized participants (n=200) was the same as the number which was used for the power determination, the potential for an underpowered study caused by dropouts (11%) cannot be ruled out.

The two main cost studies^{15,16} were conducted in different countries and used value estimates that were based on costs of therapy many years in the past. Therefore, it is uncertain whether the conditions and protocols of the study setting, as well as the historical costs values will apply to the current Canadian context. Although, one RCT⁵ performed an economic evaluation, the study was not powered to detect differences in costs, and the methods of economic evaluation was not well-reported.

The prevalence and susceptibility of pathogens to antimicrobial therapy can vary from places to place. Therefore, the generalizability of the recommendations of the included guidelines^{8,17,18} to Canada is uncertain since they were developed in other countries based on studies that were also conducted outside Canada.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The test-of cure results from a network meta-analysis in a systematic review¹³ suggest that the efficacy of daptomycin to treat acute bacterial skin and skin structure infections (ABSSSI), including ABSSSI caused by MRSA, was not statistically different from that of vancomycin and other novel antimicrobial agents such as linezolid and oritavancin. In addition, one review of meta-analyses⁶ and one systematic review³ found no significant difference in clinical outcomes between daptomycin, linezolid and vancomycin for the treatment of MRSA infections, including skin and soft tissue infections (SSTI). Among patients with complicated skin and skin structure infections (cSSSI) caused by MRSA, one RCT⁵ reported no significant difference between daptomycin, linezolid and vancomycin with regards to infection related length of stay (IRLOS) in hospital, total length of stay, medical resource utilization, and clinical response measures such as cure, improvement, no improvement, or failure. Another RCT⁷ found that daptomycin was non-inferior to vancomycin for the treatment of cSSSI among patients who were treated in the observational unit of an emergency department, and, one RCT¹⁴ found no significant difference between daptomycin and vancomycin as supplemental prophylaxis to reduce the incidence of surgical site infections caused Gram-positive pathogens, including MRSA.

In the included cost studies,^{15,16} daptomycin was not found to be more cost-effective than comparators (vancomycin and linezolid). In many of the primary studies of a systematic review of pharmacoeconomic studies¹⁵ linezolid dominated both daptomycin and vancomycin. However, in another economic evaluation,¹⁶ daptomycin, was more cost-effective than linezolid, although vancomycin was the most cost-effective among the three interventions. The significance of the therapy cost differences was not discussed. In both studies,^{15,16} hospitalization costs was the most important driver of total costs, and not the cost of drug acquisition. One RCT⁵ reported comparable cost-effectiveness between daptomycin and vancomycin. However this study was not powered to detect differences in cost between treatment arms.

Overall, the efficacy of daptomycin for the treatment of bacteremia or other infections caused by MRSA was comparable to other MRSA-active antibiotics such as vancomycin and linezolid. There was no conclusive evidence of superior cost-effectiveness of one antibiotic over the other.

PREPARED BY:

Canadian Agency for Drugs and Technologies in Health

Tel: 1-866-898-8439

www.cadth.ca

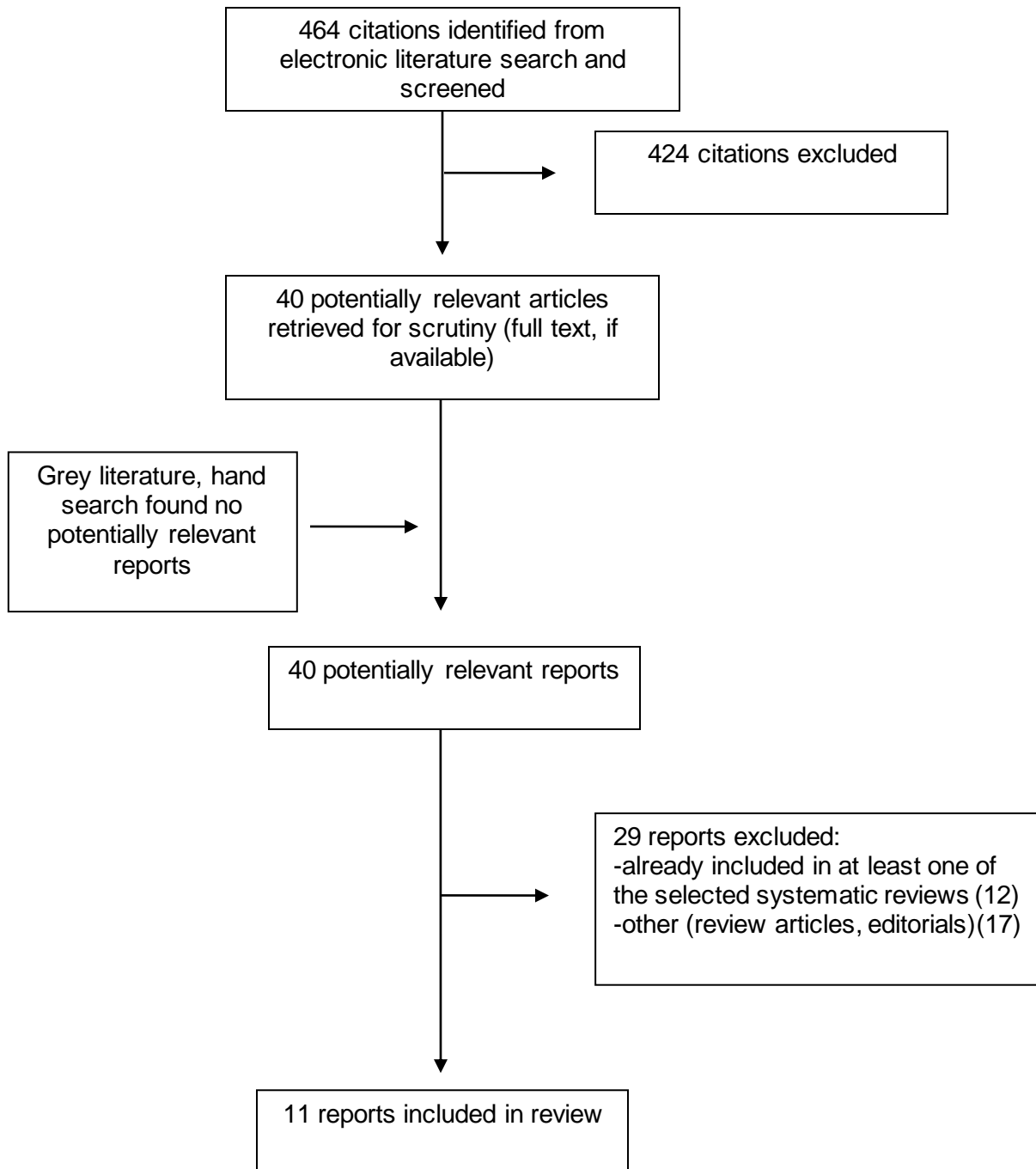
REFERENCES

1. Staphylococcus aureus. Pathogen safety data sheet - infectious substances [Internet]. Ottawa: Public Health Agency of Canada; 2012 Apr 30. [cited 2016 Jan 20]. Available from: <http://www.phac-aspc.gc.ca/lab-bio/res/psds-ftss/staphylococcus-aureus-eng.php>
2. Simor AE, Williams V, McGeer A, Raboud J, Larios O, Weiss K, et al. Prevalence of colonization and infection with methicillin-resistant Staphylococcus aureus and vancomycin-resistant Enterococcus and of Clostridium difficile infection in Canadian hospitals. Infect Control Hosp Epidemiol [Internet]. 2013 Jul [cited 2016 Jan 20];34(7):687-93. Available from: <http://www.jstor.org/stable/pdf/10.1086/670998.pdf?acceptTC=true>
3. Holland TL, Arnold C, Fowler VG, Jr. Clinical management of Staphylococcus aureus bacteremia: a review. JAMA [Internet]. 2014 Oct 1 [cited 2015 Dec 17];312(13):1330-41. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4263314>
4. Methicillin-resistant staphylococcus aureus: an update. TIBDN Newsletter [Internet]. 2012 Feb [cited 2016 Jan 20];4(3). Available from: http://microbiology.mtsinai.on.ca/research/tibdn/tibdnnews/TIBDN_Newsletter_16.pdf
5. Kauf TL, McKinnon P, Corey GR, Bedolla J, Riska PF, Sims M, et al. An open-label, pragmatic, randomized controlled clinical trial to evaluate the comparative effectiveness of daptomycin versus vancomycin for the treatment of complicated skin and skin structure infection. BMC Infect Dis [Internet]. 2015 [cited 2015 Dec 17];15:503. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4637139>
6. Tsoulas C, Nathwani D. Review of meta-analyses of vancomycin compared with new treatments for Gram-positive skin and soft-tissue infections: Are we any clearer? Int J Antimicrob Agents. 2015 Jul;46(1):1-7.
7. Shaw GJ, Meunier JM, Korfhagen J, Wayne B, Hart K, Lindsell CJ, et al. Randomized controlled noninferiority trial comparing daptomycin to vancomycin for the treatment of complicated skin and skin structure infections in an observation unit. J Emerg Med. 2015 Dec;49(6):928-36.
8. Gudiol F, Aguado JM, Almirante B, Bouza E, Cercenado E, Dominguez MA, et al. Diagnosis and treatment of bacteremia and endocarditis due to Staphylococcus aureus. A clinical guideline from the Spanish Society of Clinical Microbiology and Infectious Diseases (SEIMC). Enferm Infecc Microbiol Clin. 2015 Nov;33(9):625.
9. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol [Internet]. 2007 [cited 2016 Oct 2];7:10. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1810543/pdf/1471-2288-7-10.pdf>

10. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* [Internet]. 1998 Jun [cited 2016 Jan 21];52(6):377-84. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf>
11. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ* [Internet]. 1996 Aug 3 [cited 2016 Jan 20];313(7052):275-83. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2351717>
12. Brouwers M, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in healthcare. *CMAJ* [Internet]. 2010 Dec [cited 2016 Jan 21];182(18):E839-E842. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3001530/pdf/182e839.pdf>
13. Thom H, Thompson JC, Scott DA, Halfpenny N, Sulham K, Corey GR. Comparative efficacy of antibiotics for the treatment of acute bacterial skin and skin structure infections (ABSSSI): a systematic review and network meta-analysis. *Curr Med Res Opin* [Internet]. 2015 Aug [cited 2015 Dec 18];31(8):1539-51. Available from: <http://www.tandfonline.com/doi/pdf/10.1185/03007995.2015.1058248>
14. Stone PA, AbuRahma AF, Campbell JR, Hass SM, Mousa AY, Nanjundappa A, et al. Prospective randomized double-blinded trial comparing 2 anti-MRSA agents with supplemental coverage of cefazolin before lower extremity revascularization. *Ann Surg*. 2015 Sep;262(3):495-501.
15. Bounthavong M, Hsu DI. Cost-effectiveness of linezolid in methicillin-resistant *Staphylococcus aureus* skin and skin structure infections. *Expert Rev Pharmacoecon Outcomes Res*. 2012 Dec;12(6):683-98.
16. Wright BM, Eiland EH, III. Retrospective analysis of clinical and cost outcomes associated with Methicillin-Resistant *Staphylococcus aureus* complicated skin and skin structure infections treated with daptomycin, vancomycin, or linezolid. *J Pathog* [Internet]. 2011 [cited 2015 Dec 17];2011:347969. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3335594/pdf/JPATH2011-347969.pdf>
17. Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis* [Internet]. 2014 Jul 15 [cited 2016 Jan 7]. Available from: <http://cid.oxfordjournals.org/content/early/2014/06/14/cid.ciu296.full.pdf+html>
18. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis* [Internet].

- 2011 [cited 2016 Jan 8]. Available from:
<http://cid.oxfordjournals.org/content/early/2011/01/04/cid.ciq146.full.pdf+html>
19. Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis* [Internet]. 2014 Jul 15 [cited 2015 Dec 17];59(2):e10-e52. Available from:
<http://cid.oxfordjournals.org/content/59/2/147.full.pdf+html>
 20. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children: executive summary. *Clin Infect Dis* [Internet]. 2011 Feb 1 [cited 2015 Dec 17];52(3):285-92. Available from:
<http://cid.oxfordjournals.org/content/52/3/285.full.pdf+html>

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Types and numbers of primary studies included	Population Characteristics	Intervention ^a	Comparator(s) ^a	Clinical Outcomes, Length of Follow-Up
Thom, 2015 ¹³ UK and USA	A total of 52 trials unique RCTs were included. Forty-four trials were reported by 48 full-text articles reporting, and 8 trials were reported by 10 conference abstracts	Adult patients with ABSSSI	Vancomycin	Multiple comparators including ceftaroline; daptomycin, linezolid, oritavancin, and Tigecycline	Treatment successes at the TOC visit, 7 to 14 days after the end of treatment; ECR outcomes and incidence of AEs.
Tsoulas, 2015 ⁶ Greece and The United Kingdom	21 MAs	Patients with Gram-Positive SSTI and MRSA SSTI	Daptomycin	Anti-staphylococcal penicillins and glycopeptides	Clinical and microbiological end-points and treatment-related AEs.
Holland, 2014 ³ USA	81 studies. Summaries were available for only those with grade category of high or low, including eight (an open-label RCT, 4 cohort, and 2 case-control studies) published from 2006 to 2014 which evaluated daptomycin.	For the 8 daptomycin studies – 1355 patients with <i>S. aureus</i> bacteremia. The mean age was from 50.5 years to 67.2 years across studies/treatment arms	Daptomycin administered in doses ranging from 6mg/kg/day to 10mg/kg/day (where reported)	<ul style="list-style-type: none"> Gentamycin plus Anti-staphylococcal penicillins (for MSSA) Vancomycin (for MRSA) Comparator doses were not reported	<ul style="list-style-type: none"> Clinical response <ul style="list-style-type: none"> cure, improvement, Duration of antibiotic therapy, length of stay in hospital; Clinical failure <ul style="list-style-type: none"> mortality, persistent or recurrence bacteremia Adverse events

ABSSSI = acute bacterial skin and skin structure infections; AE= adverse events; cSSSI= complicated skin and skin structure infection ECR = Early Clinical Response; MA = meta-analysis; MRSA = methicillin resistant *Staphylococcus aureus*; IT = intention to treat; MA = meta-analysis; RCT = randomized controlled trial; MSSA = methicillin sensitive *Staphylococcus aureus*; SSTI = skin and soft tissue infection; TOC = Test-Of-Cure;

^a To answer the specific questions of this review, content of this table has been limited to included studies in which daptomycin was a treatment.

Table A2: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
Kauf, 2015 ⁵ USA	Multicenter (n=36) sites open-label, pragmatic RCT	250 enrolled patients, deemed by the investigator to need IV anti-MRSA antibiotic treatment, Age mean varied from 47.2 ± 15.2 to 50.0 ± 13.5 years across treatment groups.	IV Daptomycin 4 mg/kg once daily	IV Vancomycin (dosed at the investigator's discretion according to institutional protocol)	The primary study end point was infection-related length of stay (IRLOS). Secondary end points included health care resource utilization, cost, clinical response, and patient-reported outcomes.
Shaw, 2015 ⁷ USA	Open-label single-center RCT	100 patients admitted to an ED-based observational unit with a diagnosis of cSSSI. Mean age was 40 ± 13 years	Daptomycin given in a one-time dose of 4 mg/kg	Vancomycin given in a dose of 15 mg/kg at baseline and again at 12 h for a maximum of 2 doses	To meet observation unit discharge criteria ^a without needing a subsequent change in antibiotic therapy and without requiring a return to the ED for the same infection within 30 days
Stone, 2015 ¹⁴ USA	Single-center prospective double blinded RCT	200 patients ≥ 18 years of age undergoing a groin or lower extremity procedure or elective arterial revascularization	Vancomycin plus Cefazolin	Daptomycin plus Cefazolin during their surgical procedure.	Reduction of postoperative infections as determined by surgical site infection 90 days after of the index procedure.

ABSSSI = acute bacterial skin and skin structure infections; AE= adverse events; cSSSI= complicated skin and skin structure infection ECR = Early Clinical Response; ED = emergency department; IV = intravenous; MA = meta-analysis; MRSA = methicillin resistant *Staphylococcus aureus*; ITT = intention to treat; MA = meta-analysis; RCT = randomized controlled trial; MSSA = methicillin sensitive *Staphylococcus aureus*; SSTI = skin and soft tissue infection; TOC = Test-Of-Cure;

^a Observation unit discharge criteria were defined as stable vital signs (O₂ saturation > 92%, systolic blood pressure between 90 and 160 mm Hg, diastolic blood pressure < 100 mm Hg, heart rate between 50 and 100 beats/min, respiration rate < 20 breaths per minute, and temperature < 38.3°C), stable or improving clinical signs and symptoms, cellulitic lesion remaining within baseline margins (a < 10% increase from baseline), an increase of no greater than 1 in pain scale, and the ability to tolerate medications, fluids, or food orally, as documented by order of oral medication or clinical evaluation.

Table A3: Characteristics of Included Cost Studies

First author, Publication Year, Country	Type of Analysis, Perspective	Intervention, Comparator	Study Population	Time Horizon	Main Assumptions
Bounthavong, 2012 ¹⁵ Multiple countries ^a	A systematic review of 15 pharmaco-economic studies to assess the total direct costs using payers' (healthcare) perspective	Linezolid, vancomycin or daptomycin	Patients (n >16,459) ^b from with cSSTIs and cSSSI, including MRSA-related infections. Reported mean age of patients varied from 46.3 ± 12.6 years to 77.0 ± 7.3 years old.	NR. However, scenario analysis included the following changes in hospital LOS <ul style="list-style-type: none"> • Vancomycin: from 14 to 8 days • Linezolid: from 5.4 to 1.4 days • Daptomycin: from 6.8 to 4 days 	CEAC were used to evaluate the probability of a study drug's cost-effectiveness relative to a comparator across a range of WTP thresholds
Wright, 2011 ¹⁶	Single-center retrospective analysis using medical records. The perspective was not specified, however, a breakdown of the overall cost reflects only direct cost without any mention of indirect cost, which suggests a healthcare perspective.	Daptomycin, vancomycin, or linezolid.	82 hospitalized adult patients (≥ 17 years) with cSSSIs due to suspected or documented MRSA who were treated with vancomycin, linezolid, or daptomycin. The mean age ranged from 54 to 60 years.	Till discharge from hospital	NR

CEAC = cost-effectiveness acceptability curve; cSSSI= complicated skin and skin-structure infections; cSSTI = complicated skin and soft-tissue infections; LOS = length of stay; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*; NR = not reported; SSTIs = skin and soft tissue infections; WTP = willingness-to-pay

^a The pharmaco-economic studies were from Brazil, Canada, France, Germany, Mexico, The UK, and USA.¹⁵

^b Sample sizes were not reported for five included primary studies

Table A4: Characteristics of Included Guidelines

Objectives			Methodology			
Intended users/ Target population	Intervention and Practice Considered	Major Outcomes Considered	Evidence collection, Selection and Synthesis	Evidence Quality and Strength	Recommendations development and Evaluation	Guideline Validation
Gudiol, 2015 ^o – Spanish Society of Clinical Microbiology and Infectious Diseases (SEIMC)						
Clinicians/ patients with SAB (clinically suspicious or confirmed)	Evidence-based guidelines to improve the diagnosis and treatment of bacteremia and IE caused by <i>S. aureus</i> , including the management of clinical suspicion of SAB, confirmed SAB, (non-complicated and complicated) and staphylococcal IE	<ul style="list-style-type: none"> • Effectiveness of treatment of <ul style="list-style-type: none"> ○ clinical suspicion of SAB ○ non-complicated SAB (primary SAB and CRB) • Effectiveness of clinical and microbiological evaluation of complicated SAB • Effectiveness of managing <ul style="list-style-type: none"> ○ complicated SAB caused by MSSA or MRSA ○ IE caused by <i>S. aureus</i> 	Evidence was collected from systematic search and critical review of literature and the opinion of experts, who are SEIMC members	Recommendations were supported by scientific evidence ranked as follows I: Evidence obtained from ≥1 randomized clinical trial II: Evidence obtained from ≥1 well-designed non-randomized clinical trial, or cohort studies, or case-control-studies, especially if they have been performed in more than one center. III: Evidence obtained from documents or opinions of experts, based in clinical experience or case series	Recommendations were graded as follows: A: Good evidence to recommend the use of a measure or practice B: Moderate evidence to recommend the use of a measure or practice C: Poor evidence to recommend the use of a measure or practice D: Moderate evidence to discourage the use of a measure or practice E: Good evidence to discourage the use of a measure or practice	Recommendations have been agreed by all the authors and the coordinators of the Statement. The manuscript was open to suggestions and comments by any of the SEIMC members before publication of the final document.

Table A4: Characteristics of Included Guidelines

Objectives			Methodology			
Intended users/ Target population	Intervention and Practice Considered	Major Outcomes Considered	Evidence collection, Selection and Synthesis	Evidence Quality and Strength	Recommendations development and Evaluation	Guideline Validation
Stevens, 2014 ¹⁹ – Infectious Diseases Society of America						
Clinicians/ Patients with SSTIs caused by various pathogens including MSSA or MRSA	Evidence-based guidelines for the diagnosis, and appropriate treatment of diverse SSTIs including minor superficial infections and life-threatening infections.	Appropriateness of the evaluation and treatment of <ul style="list-style-type: none"> • purulent and non-purulent SSTIs • recurrent skin abscesses • surgical site infections 	Systematic review and analysis of literature from relevant databases. Evidence was gathered from RCTs, abstracts from national meetings, observational studies, and case series and combined with the opinion of the expert panel members	The quality of evidence was systematically ranked as High: Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies Moderate: Evidence from RCTs with important limitations (inconsistent results, indirect or imprecise evidence, methodological flaws) or exceptionally strong evidence from unbiased observational studies Low: Evidence for at least 1 critical outcome from observational studies, RCTs with serious flaws or indirect evidence;	The strength of recommendation was graded based on the quality of evidence. Some grade categories are as follows: Strong recommendation, high-quality evidence: can apply to most patients in most circumstances. Further research is unlikely to change confidence in the estimate of effect Strong recommendation, low-quality evidence: may change when higher-quality evidence becomes available. Further research is likely to have an important impact on confidence in the estimate of effect Weak	A panel of 10 multidisciplinary experts in the management of SSTIs in children and adults reviewed all recommendations, for strength, and quality of evidence, and resolved all discrepancies by consensus. The guideline was reviewed and approved by the IDSA SPGC and Board of Directors and endorsed by PIDS.

Table A4: Characteristics of Included Guidelines

Objectives			Methodology			
Intended users/ Target population	Intervention and Practice Considered	Major Outcomes Considered	Evidence collection, Selection and Synthesis	Evidence Quality and Strength	Recommendations development and Evaluation	Guideline Validation
				and Very low: Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence	recommendation, high-quality evidence: The best action may differ depending on circumstances or patient's or societal values. Further research is unlikely to change confidence in the estimate of effect	
Liu, 2011 ²⁰ – Infectious Diseases Society of America						
Clinicians/ Patients (adults and children) with MRSA infections	Evidence-based guidelines to provide recommendations for the management of MRSA infections	Effectiveness of managing <ul style="list-style-type: none"> • Recurrent MRSA SSTIs • MRSA bacteremia and IE • MRSA pneumonia • MRSA bone infections • MRSA infections of the CNS 	Systematic review and analysis of literature from relevant databases. Evidence was gathered from RCTs, abstracts from national meetings, observational studies, and case series and combined with the opinion of the expert panel members.	The quality of evidence was systematically ranked as I: Evidence from at least one properly randomized, controlled trial. II: Evidence from at least one well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from > 1 center); from multiple time-series; or from dramatic results from	The strength of the recommendations was graded as follows: A: Good evidence to support a recommendation for or against use. B: Moderate evidence to support a recommendation for or against use. C: Poor evidence to support a recommendation.	All members of the panel participated in the preparation and review of the draft guideline. The guideline was reviewed and endorsed by the PIDS, ACEP, and AAP; and it was reviewed and approved by the IDSA SPGC and the IDSA Board of Directors prior to dissemination.

Table A4: Characteristics of Included Guidelines

Objectives			Methodology			
Intended users/ Target population	Intervention and Practice Considered	Major Outcomes Considered	Evidence collection, Selection and Synthesis	Evidence Quality and Strength	Recommendations development and Evaluation	Guideline Validation
				uncontrolled experiments. III: Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.		

AAP= American Academy of Pediatrics; ACEP = American College of Emergency Physicians; CPG = clinical practice guideline; CRB = catheter-related bacteremia; GRADE = grading of recommendations assessment, development, and evaluation; IDSA = Infectious Diseases Society of America; IE =infective endocarditis; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*; PIDS = Pediatric Infectious Diseases Society; *S. aureus* = *Staphylococcus aureus*; SAB = *S. aureus* bacteremia; SPGC = Standards and Practice Guidelines Committee; SSTs =skin and soft tissue infections;

APPENDIX 3: Critical Appraisal of Included Publications

Table A5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR⁹

Strengths	Limitations
Thom, 2015 ¹³	
<ul style="list-style-type: none"> The study objectives and the inclusion and exclusion criteria were clearly described and the RCTs that met the criteria were identified through comprehensive systematic searches of relevant databases. The risk of bias of the included full publications was assessed using the Cochrane risk of bias tool. The included primary studies were generally judged to be at low risk of bias Treatment doses and administration across trials were considered clinically homogenous The studies included in the NMA were summarized in a table. 	<ul style="list-style-type: none"> The selection process of the included studies was not well reported. Only two (n=175) of the 35 included studies involved daptomycin as treatment, with the key pathogens identified as MSRA in one and as Staphylococcus aureus in the other. It is unknown if there was enough information to conclusively answer the relevant research questions of this review. Daptomycin was compared directly with only vancomycin. There was no study which directly compared daptomycin and any of the newer antibiotics for the MRSA and MSSA. Thus, it is difficult to draw a conclusion about the comparative effectiveness of these therapies. This was an industry funded research, and some of the investigators were employees or paid consultants of pharmaceutical companies.
Tsoulas, 2015 ⁶	
<ul style="list-style-type: none"> The study objectives and the inclusion and exclusion criteria were clearly described. A comprehensive search of relevant databases was conducted to identify the MA that met the inclusion criteria. This review of meta-analysis received no funding support, although one of the two co-authors had been a member of advisory boards for several pharmaceutical companies, and had received research and lecture funds. 	<ul style="list-style-type: none"> The selection process of the included MA was not well reported. The included MAs were not assessed for quality. Therefore, it is difficult to assess the rigor of the conclusions of this review based on the strength of evidence. The method for combining the results of the included MAs was not well-described; thus making it difficult to assess for quality. There are no head-to-head trials of newer antibiotics including daptomycin. The estimated relative treatment effects of these drugs were derived from indirect comparisons, and thus have uncertain precision.
Holland, 2014 ³	
<ul style="list-style-type: none"> The study objectives and the inclusion and exclusion criteria were clearly described. A comprehensive search of relevant databases was conducted to identify the included primary studies. 	<ul style="list-style-type: none"> Overall, data quality was poor, with only one of the 81 included primary studies meeting the criteria for high quality evidence; even so, it was an open-label RCT. The conclusion of the study was dependent on one high quality open-label RCT. Thus it appears further more rigorous studies may

Table A5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR⁹

Strengths	Limitations
<ul style="list-style-type: none"> The included studies were graded by consensus of independent reviews by two authors, resolving disagreements through a resolution review by a third author The study was not funded by industry. However, both authors had been paid consultants for pharmaceutical companies, and one had received grant support from industry. 	<p>be needed to confirm the conclusion.</p>

Table A6: Strengths and Limitations of Randomized Controlled Trials using Downs and Black¹⁰

Strengths	Limitations
<ul style="list-style-type: none"> Kauf, 2015⁵ Inclusion and exclusion criteria were clearly defined Patients' characteristics were described and there were no significant differences between the treatment arms at baseline. Sample size calculation was done to ensure the study had sufficient power to detect differences in the primary endpoint between the two interventions All potential confounding variables were included at model entry and were retained in the model if the associated P value was < 0.05; and were analyzed to determine appropriate inclusion in the multivariate analyses of IRLOS, total LOS, total inpatient cost, and clinical success. 	<ul style="list-style-type: none"> The study had an open-label design which may have impacted the assessment of clinical response since randomization to interventions was unblinded. However, the primary point (IRLOS) was objectively defined and unlikely to be significantly affected by the design. The pragmatic nature of the study allowed flexibility the introduced imbalances that could bias the study findings. For example, only the first study drug dose was required by the protocol; all subsequent care decisions were at the discretion of the treating physician and local hospital practice, without restrictions regarding concomitant medications, adjunctive procedures or other therapy, conversion from IV to oral therapy and treatment discontinuation. The primary analytic sample included all patients with data available to calculate the primary end point (IRLOS). There was no accounting to missing data. Thus it is unknown if the randomization effect at baseline was maintained through the analysis. Cultures were not obtained for all patients, therefore the risk of imbalance MSSA that favors the daptomycin arm cannot be ruled out, since vancomycin has been associated with increased risk for

Table A6: Strengths and Limitations of Randomized Controlled Trials using Downs and Black¹⁰

Strengths	Limitations
	<p>treatment failure in MSSA infections compared with other antibiotics.</p> <ul style="list-style-type: none"> The authors were employee/consultants of, or individuals who had received research grant from a pharmaceutical company
Shaw, 2015 ⁷	
<ul style="list-style-type: none"> The inclusion and exclusion criteria of the study were clearly defined Details of the demographic characteristics of the patients, their medical history, and presenting vital signs were provided, and they were generally similar across the two groups 	<ul style="list-style-type: none"> The study had an open-label design which may have impacted the assessment of clinical response since randomization to interventions was unblinded. No mechanism was in place to ensure patients compliance with antibiotic therapy after discharge from the observational unit. Therefore, the reliability of study end-points, which were assessed 30 days after participants departed the observation unit, is uncertain. The study was funded by a pharmaceutical company, although the authors stated that the company had no control over the design, conduct, analysis, or reporting of results.
Stone, 2015 ¹⁴	
<ul style="list-style-type: none"> Participants were randomized in a blinded manner and treatment assignments were concealed using similar appearing bags and sizes for the two treatments. There were no differences between the patients in either study arm with respect to age, sex, race/ethnicity, co-morbid conditions, or perioperative risk factors. The objectives of the study, as well as the inclusion and exclusion criteria were specified. A sample size was determined by calculation to ensure the study had sufficient power to detect differences in the primary endpoint between the two interventions The authors declare no conflicts of interest. 	<ul style="list-style-type: none"> A substantial proportion (11%) of the participants was not included in the analysis, and the missing data was not accounted for. Although the study was well powered at baseline, the number of randomized participants (n=200) was the same as the sample size used to make that determination. Therefore, the potential for an underpowered study caused by dropouts (11%) cannot be ruled out.

Table A7: Strengths and Limitations of Economic Studies using Drummond¹¹

Strengths	Limitations
Bounthavong, 2012 ¹⁵	
<ul style="list-style-type: none"> • This was a systematic review of pharmacoeconomic studies with a well-defined objective, and stated viewpoint for performed analyses • Included studies were selected after a comprehensive literature search and the type of studies upon which the economic evaluations were based was described along with the competing alternative interventions. • The sources of the cost estimates were published literature or national database, which are likely to be credible 	<ul style="list-style-type: none"> • Details of the studies from which data were used for the economic evaluations were not given. Therefore, the applicability of the study protocols to regular practice, including the used doses of alternative interventions and the general quality of care across study groups could not be assessed for potential biases. • The analysis was based on the payer's (healthcare system's) perspective, which does not include indirect costs, patient out-of-pocket costs or quality-adjusted life years. • Only the final direct costs were given for each intervention. Thus, it was difficult to assess whether the included cost items were appropriate, and to ascertain their generalizability to the Canadian context. • The values of cost estimates were adjusted for a period now in history, and were not discounted to the present value. Therefore, it is unknown if they are currently applicable. • One of the included studies evaluated the cost of the alternative interventions as second line therapy after treatment with a comparator had failed. This model is not very practical for first-line therapy (which is the usual goal of therapy selection) but may be considered in a rescue situation. • One of the two researchers had received grants from pharmaceutical companies and other was on the speaker's panel for some pharmaceutical companies. They declared that apart from these, there were no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

Wright, 2011¹⁶

- | | |
|---|---|
| <ul style="list-style-type: none"> • The study had a well-defined objective. The competing alternative interventions were clearly defined, including the daily dose upon which cost evaluation was based. • Actual hospital records were the sources of the cost estimates, thereby eliminating potential errors (under-or over-estimations) that may be associated with literature sources and projections. • The cost of therapy was itemized to facilitate the assessment of the contributions of the various aspects of the therapies to the final value. • The authors declared that no funding was sought; however, one of the two authors served on the speaker's bureau for a pharmaceutical company. | <ul style="list-style-type: none"> • Although the total average daily dose of interventions for which cost was determined was provided, this was not sufficient to assess the propriety of dosing relative to regular practice, because the recommended dosing of interventions is based on specific criteria including bodyweight. • The perspective of the economic analysis was not specified. However, the breakdown of the cost of therapy indicates that the study assumed a payer's perspective, which does not include indirect costs, patient out-of-pocket costs or quality-adjusted life years. Therefore, the total cost of the intervention is unknown. • The analysis was based on historical cost without discounting for the future. Therefore, it is unknown if the cost estimates of the interventions are currently applicable. • The study was based on records of a single hospital in the USA. Therefore, the generalizability of the included cost to the Canadian context is unknown. |
|---|---|

cSSSI = complicated skin and skin-structure infections; cSSTI = complicated skin and soft-tissue infections; IRLLOS = infection-related length of stay; LOS = length of stay; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*; SSTIs = skin and soft tissue infections;

Table A8: Strengths and Limitations of Guidelines using AGREE II¹²

Strengths	Limitations
Gudiol, 2015 ⁸	
<ul style="list-style-type: none"> • The objectives, targeted users and population to whom it was meant to apply were well-described. • Relevant databases were systematically searched electronically and manually to collected evidence. • The quality and strength of evidence were reported using a clearly described rating scheme. • The recommendations were reached by consensus among expert. • The strength of each recommendation was linked to supporting evidence. • The manuscript was open to suggestions and comments from SEIMC members before publication of the final document, and the recommendations were approved by the appropriate executive body in SEIMC 	<ul style="list-style-type: none"> • Criteria for evidence selection, and procedure for updating the guideline were not available for assessment. • There was no evidence that the guideline was externally validated. Furthermore, the input of the target population (patients, the general public) was not sought by guideline developing panel. However, specialized nature of the professional body that commission the development of the guideline and approved its recommendation suggest a superior external review was that it was unlikely, and lack of target population input was unlikely reduce the strength and quality of the recommendations, given the technical nature of the subject matter. • The guideline was developed in Spain to guide practice in that country. Therefore, considering that microbial susceptibility to antibiotic therapy can vary from on geographical region to another, even within one country, the generalizability of the recommendations of the guideline in Canada is uncertain. • Members of the guideline developing panel had either received academic grants, and/or been a consultant or speaker for some pharmaceutical company.
Stevens, 2014 ¹⁷	
<ul style="list-style-type: none"> • The objectives, targeted users and population to whom it was meant to apply were well-described. • Relevant databases were systematically searched electronically and manually to collected evidence. • The quality and strength of evidence were reported using a clearly described rating scheme. • The recommendations were reached by consensus among expert. • The strength of each recommendation was linked to supporting evidence. • The guidelines were validated internally by 	<ul style="list-style-type: none"> • The strength and quality of the recommendation were described with a pair of words chosen from strong, moderate, high, week, low and very low. Although, an interpretation scheme was provided for the ranking, it was still difficult to follow. • Some quality measures such as criteria for selection of evidence, procedure for updating the guideline, which are determinants of the rigor of processes and procedures for the development of the guideline, were not available for assessment. • The input of the target population (patients, the general public) was not sought guideline developing panel. However, this may not reduce the strength quality of the recommendations given the technical nature of

Table A8: Strengths and Limitations of Guidelines using AGREE II¹²

Strengths	Limitations
<p>experts, endorsed by PIDS, and approved by the Executive Board of IDSA.</p>	<p>the subject matter.</p> <ul style="list-style-type: none"> • The guideline was developed in the USA to guide practice in that country. Therefore, considering that microbial susceptibility to antibiotic therapy can vary from one geographical region to another, even within one country, the generalizability of the recommendations of the guideline in Canada is uncertain. • Each member of the guideline developing panel had either received academic grants, and/or been a consultant or speaker for some pharmaceutical company.
<p>Liu, 2011¹⁸</p>	
<ul style="list-style-type: none"> • The objectives, targeted users and population to whom it was meant to apply were well-described. • Relevant databases were systematically searched electronically and manually to collect evidence. • The quality and strength of evidence were reported using a clearly described rating scheme. • The recommendations were reached by consensus among experts. • The strength of each recommendation was linked to supporting evidence. • The guidelines were validated internally by experts, endorsed by ACEP, PIDS, and approved by the Executive Board of IDSA. 	<ul style="list-style-type: none"> • Some quality measures such as criteria for selection of evidence, procedure for updating the guideline, which are determinants of the rigor of processes and procedures for the development of the guideline, were not available for assessment. • The input of the target population (patients, the general public) was not sought guideline developing panel. However, this may not reduce the strength quality of the recommendations given the technical nature of the subject matter. • The guideline was developed in the USA to guide practice in that country. Therefore, considering that microbial susceptibility to antibiotic therapy can vary from one geographical region to another, even within one country, the generalizability of the recommendations of the guideline in Canada is uncertain. • Each member of the guideline developing panel had either received academic grants, and/or been a consultant or speaker for some pharmaceutical company.

AAP= American Academy of Pediatrics; ACEP = American College of Emergency Physicians; IDSA = Infectious Diseases Society of America; PIDS = Pediatric Infectious Diseases Society; SEIMC = Spanish Society of Clinical Microbiology and Infectious Diseases

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A9: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
<p>Thom, 2015¹³</p> <ul style="list-style-type: none"> • Daptomycin was not significantly different from vancomycin and the other antibacterial agents with regards to the TOC results in the treatment of patients with ABSSSI. • The mean (95% CrI) OR for the antimicrobial agents relative to vancomycin were: daptomycin 2.18 (0.90, 5.42); linezolid 1.55 (0.91, 2.57); and oritavancin 1200 mg 1.06 (0.80, 1.43). • The mean (95% CrI) OR for the antimicrobial agents relative to vancomycin in the MRSA sub-group were: daptomycin 0.74 (0.13, 3.66); linezolid 1.55 (0.96, 2.46); and oritavancin 1200 mg 0.94 (0.44, 2.02). 	<ul style="list-style-type: none"> • “The results suggest equivalence of clinical efficacy between vancomycin, daptomycin, linezolid, and novel antimicrobial agents including oritavancin for the treatment of ABSSSI at TOC.”¹³ page 1539
<p>Tsoulas, 2015⁶</p> <ul style="list-style-type: none"> • Meta-analysis results showed that the clinical and micrological success rate in treating SSTI and cSSSI with daptomycin was not statistically significant different that of comparators (vancomycin and linezolid). The OR(95% CI) was 1.05 (0.84, 1.31) for clinical success and 1.05 (0.61, 1.79) for microbiological success. Results were consistent in the subgroups of MRSA. • The safety of daptomycin was similar to comparators with regard to treatment-related AEs with OR (95%CI) of 1.06 (0.71, 1.59) • Although daptomycin demonstrated a trend towards less treatment discontinuations or mortality, the difference was not statistically significant (OR [95% CI] = 0.71 [0.46–1.10]). • Specific AE related to the use of daptomycin was creatine phosphokinase (CPK) elevations. • Some evidence suggests that daptomycin could be associated with reduced treatment duration, and linezolid with 	<ul style="list-style-type: none"> • “MAs do not provide sufficient data to support the use of other agents over vancomycin. The availability of several treatment options for Gram-positive SSTIs should allow physicians to make individualized treatment decisions based on the available evidence and the specific characteristics of their individual patients. Future studies should be encouraged to include clinical and cost-effectiveness data to address many of the questions raised in these analyses. In addition, non-pharma sponsored studies and head-to-head trials of newer antimicrobials will allow more appropriate between-treatment comparisons.”⁶ page 7

Table A9: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
<p>reduced length of intravenous treatment and reduced hospital length of stay compared with vancomycin.</p>	
Holland, 2014 ³	
<ul style="list-style-type: none"> • Daptomycin was non-inferior to vancomycin for the treatment of MRSA bacteremia (and SAB in penicillin-allergic patients) with or without endocarditis. • Treatment of MSSA bacteremia with resulted daptomycin achieved comparable success rate (44.2%) as to low-dose, short course gentamicin plus an anti-staphylococcal penicillin (41.7%), absolute difference (95% CI) 2.4%, (-10.2, 15.1) 	<ul style="list-style-type: none"> • “Vancomycin and daptomycin remain the first-line therapies for MRSA bacteremia. Treatment should extend for at least 14 days from the first negative blood culture, and it should be longer in those with complicated disease. High quality trials comparing treatment strategies, antibiotics, and treatment durations are needed to optimize the management of this common, serious infection.”³ page 9
Kauf, 2015 ^{5 a}	
<ul style="list-style-type: none"> • In unadjusted analysis a greater proportion of daptomycin-treated than vancomycin-treated patients achieved clinical success by day 2 (83% versus 74%) and day 3 (86% versus 83%, although the differences did not reach the level of statistical. • A logistic regression analysis showed that treatment with vancomycin was associated with a decreased chance of achieving clinical success within 2 days compared with daptomycin treatment, (O = 0.498; 95 % CI: 0.249, 0.997; P = 0.049). • All patients in each treatment group reached clinical success by the end of their inpatient stay, 	<ul style="list-style-type: none"> • “This study did not provide conclusive evidence of the superiority of one treatment over the other in terms of clinical, economic, or patient outcomes. The data suggest that physician and patient preference, rather than drug acquisition cost, should be the primary driver of initial antibiotic selection for hospitalized patients with cSSSI.”⁵ page 1
Shaw, 2015 ⁷	
<ul style="list-style-type: none"> • There was no significant difference between daptomycin and vancomycin with regards to treatment success or failure. • 30% of patients in the daptomycin-treated group met the objective discharge criteria and required no change in antibiotic therapy within 30 days compared with 28% of patients in the vancomycin-treated group. • 70% Of patients in the daptomycin-treated group were classified as treatment failure compared with 72% of patients 	<ul style="list-style-type: none"> • “Our results suggest that daptomycin is non-inferior to vancomycin for the treatment of cSSSI in observation unit patients. Secondary outcomes and adverse event rates did not differ between the two study arms. We conclude that daptomycin may be used in place of vancomycin to treat cSSSI.”⁷ page934

Table A9: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
<p>in the vancomycin-treated group (difference in proportions 2%; 95% CI: 20, 16).</p> <ul style="list-style-type: none"> • The relative risk (95% CI) of meeting the primary endpoint, daptomycin versus vancomycin, was 1.07 (0.58, 1.98), suggesting no difference in outcome for the two treatments • Since the CI did not exceed the non-inferiority margin (30%), daptomycin is not inferior to vancomycin for the treatment of cSSSI in the observation unit. • The incidence of reported AEs was 8% in the daptomycin group and 14% in the vancomycin group. There were no serious adverse events reported. 	
Stone, 2015 ¹⁴	
<ul style="list-style-type: none"> • The overall (both early and late infections) surgical infections rate was 14% among patients in the cefazolin plus daptomycin group compared with 9% of patients in the cefazolin plus vancomycin • Early vascular surgical site infection occurred in 11.83% of patients in the daptomycin arm compared with 8.24% of patients in the Vancomycin arm, ($P = 0.43$). • There was only one (1.08%) MRSA infections in the daptomycin group within 90 days of index procedure and none in the vancomycin group, demonstrating no significant relative advantage of one intervention over the other. • Readmissions related to surgical site infections occurred in 11.8% in the daptomycin group compared with 4.71% in the vancomycin group ($P = 0.11$). Median hospital charges related to readmissions due to a surgical site infection was \$50,823 in the combination Vancomycin arm and \$110,920 in the combination Daptomycin group; however, no statistical significance was appreciated ($P = 0.11$). 	<ul style="list-style-type: none"> • “Vancomycin supplemental prophylaxis seems to reduce the incidence of Gram-positive infection compared with adding supplemental Daptomycin prophylaxis. The incidence of MRSA-related surgical site infections is low with the addition of either anti-MRSA agents compared with historical incidence of MRSA-related infection.”¹⁴ page 495

ABSSSI = acute bacterial skin and skin structure infections; AE= adverse events; cSSSI= complicated skin and skin structure infection MA = meta-analysis; MRSA = methicillin resistant *Staphylococcus aureus*;

^a The cost outcomes of this study have also been reported in Table A10

Table A10: Summary of Findings of included Economic Studies

Main Study Findings	Author's Conclusions
Bounthavong, 2012 ¹⁵	
<ul style="list-style-type: none"> • One primary study from USA reported that the total direct costs of therapy for MRSA cSSTI was higher with daptomycin (US\$11,362) compared with linezolid (US\$8149), vancomycin (US\$8974), and tigecycline (US\$10,333). • Another primary study from USA found that linezolid was dominant compared to daptomycin for the treatment of suspected or confirmed MRSA cSSTI. However, in a sensitivity analyses where LOS associated with daptomycin therapy was changed from 6.8 to 4 days, the ICER for linezolid compared with daptomycin was US\$182,789 per additional successful cure gained. • One primary study from Mexico reported that the cost-effectiveness ratio for daptomycin and linezolid was US\$52,135.67 and US\$67,623.14 per success, respectively. • Another primary study from Mexico found that the for cSSTI, the ICERs for a second-line therapy after unsuccessful first antibiotic were US\$3255, US\$3310, US\$3310 and US\$3423 per clinical success achieved, the daptomycin - linezolid, vancomycin–daptomycin, vancomycin–linezolid and linezolid–daptomycin, respectively. Daptomycin (US\$11,362) had the highest total direct costs of treatment compared with linezolid which had the lowest cost (US\$8149) followed by vancomycin (US\$8974), and tigecycline (US\$10,333). 	<ul style="list-style-type: none"> • “Pharmacoeconomic evaluations have consistently shown that linezolid was a dominant strategy for MRSA cSSTI/cSSSI compared with comparators like vancomycin and daptomycin. This dominance is a result of at least equivalent efficacy with confirmed MRSA infection, and a shorter duration of stay derived from a reduction in treatment duration of the IV formulation, facilitating early discharge with the availability of an oral formulation that is nearly 100% bioavailable. However, it should be noted that a majority of the pharmacoeconomic studies are based on decision models that need to be validated in clinical practice. Furthermore, oral agents with significant bioavailability such as sulfamethoxazole/trimethoprim, minocycline, doxycycline and clindamycin may also be available for comparator antibiotics depending on the MRSA strain and results of antimicrobial susceptibility testing.”¹⁵ page 695

Kauf, 2015 ⁵ ^a	
<ul style="list-style-type: none"> • There was no significant difference in the primary end point (IRLOS) between the daptomycin and vancomycin arms • The mean total inpatient cost was \$9641 for the daptomycin arm and \$9083 for the vancomycin arm. • Hospital LOS contributed 85.9 % to the total hospitalization cost, compared with 6.4 % for drug costs. 	<p>“This study did not provide conclusive evidence of the superiority of one treatment over the other in terms of clinical, economic, or patient outcomes.”⁵ page 1</p>
Wright, 2011 ¹⁶	
<ul style="list-style-type: none"> • Daptomycin had a highest mean total inpatient cost (\$9641) for the treatment cSSSI caused by suspected or documented MRSA compared with vancomycin (\$9083). • The drug cost for daptomycin was significantly greater than that of vancomycin. Conversely, daptomycin was associated with lower laboratory and radiologic test costs than vancomycin (P < 0.001 for both comparisons). • Length of stay (LOS) in the hospital was the primary driver of cost in both treatment arms, contributing 85.9 % to the total hospitalization cost, compared with 6.4 % for drug costs. 	<p>“This study showed similar clinical and cost outcomes with the use of daptomycin when compared with vancomycin and linezolid in cSSSIs for a similar patient population. In addition, while daptomycin showed a slightly greater overall duration of therapy it was well tolerated and showed an overall decreased length of stay in the ward comparatively which proved to be financially advantageous considering that per diem hospital costs accounts were the most expensive healthcare resource in this study population. The retrospective design of this analysis further justifies the conclusion that future studies are necessary to determine if MRSA treatment options can be stratified based on the severity of the infectious process as to ensure that the duration of a patient’s hospitalization is optimized.”¹⁶ page 5</p>

ICER = incremental cost-effectiveness ratio; IRLOS = infection-related length of stay; LOS = length of stay; cSSSI = complicated skin and skin structure infection; MA = meta-analysis; MRSA = methicillin resistant *Staphylococcus aureus*; MSSA = methicillin sensitive *Staphylococcus aureus*; SSTI = skin and soft tissue infection; TOC = Test-Of-Cure;

^a The clinical outcomes of this study have also been reported in Table A9

Table A11: Summary of Guideline Recommendations^a

<p>Gudiol, 2015⁸</p>	<ul style="list-style-type: none"> • Daptomycin (>10mg/kg/day) in combination with cloxacillin the treatment of choice for nosocomial or health-care related infective endocarditis (IE).(B-II) • Daptomycin (>10mg/kg/day) alone or in combination with fosfomycin is an alternative treatment of infective endocarditis in patients who are allergic to β-lactam antibiotics. (B-II) may be combined with cloxacillin as alternative treatment to cloxacillin alone for complicated bacteremia caused by MSSA (A-III) • High-dose daptomycin (>10mg/kg/day) alone may be used as alternative empirical treatment of suspected MRSA bacteremia in place of a combination therapy of a penicillinase-stable β-lactam plus a second antibiotic with bactericidal activity against MRSA.(A-II) • Daptomycin may be used as alternative treatment to vancomycin (treatment of choice for catheter-related bacteremia caused by MRSA (A-I) • Daptomycin at a dose of 10mg/kg/day is the treatment of choice for complicated bacteremia caused by MRSA (A-III) • Daptomycin (≥10mg/kg/day) in combination with cloxacillin is the recommended treatment for native valve IE caused by MRSA with vancomycin MIC ≥ 1.5mg/L.(B-II)
<p>Stevens, 2014¹⁷</p>	<ul style="list-style-type: none"> • Daptomycin (4mg/kg/day) is a recommended treatment option for skin and soft tissue infections (SSTI) caused by MRSA(XYZ) (Strong, Low) • Daptomycin (4mg/kg/day) a recommended treatment option for surgical site infections where risk factors for MRSA are high (nasal colonization, prior MRSA infection, recent hospitalization, recent antibiotics).
<p>Liu, 2011¹⁸</p>	<ul style="list-style-type: none"> • Daptomycin (4mg/kg/day) is a recommended empirical treatment option for hospitalized patients with cSSSI (A-1) • Daptomycin 6 mg/kg/dose IV once daily for at least 2 weeks is a recommended treatment option for uncomplicated bacteremia. (A-I) • daptomycin 6 mg/kg/dose IV once daily for at least four to six weeks is a recommended treatment option for complicated bacteremia.(A-I) Some experts recommend higher dosage (8 to 10 mg/kg daily. (B-III) • Daptomycin 6 mg/kg/daily for 6 weeks is a recommended treatment option for IE. (A-I) Some experts recommend higher dosage (8 to 10 mg/kg daily. (B-III) • Daptomycin (6mg/kg/day) is a recommended treatments option for bone and joint infections (osteomyelitis or septic Arthritis) (B-II). • Where microbial isolate is susceptible, high-dose daptomycin (10 mg/kg/day) in combination with another agent (e.g. gentamicin 1 mg/kg IV every 8 hours) should be considered for the management of persistent MRSA bacteremia and vancomycin treatment failures (B-III) • Daptomycin (10mg/kg/day) may be combined with cloxacillin as alternative treatment to cloxacillin alone for complicated bacteremia caused by MSSA (A-III) • Daptomycin may be used as alternative treatment to cloxacillin for catheter-related bacteremia caused by MSSA (A-I)

cSSSI = complicated skin and skin structure infection; IV = intravenous; MRSA = methicillin resistant *Staphylococcus aureus*; IE = infective endocarditis; MSSA = methicillin sensitive *Staphylococcus aureus*; SSTI = skin and soft tissue infection

^a The assigned strength and quality of each recommendation (in brackets) follow the scheme already described in Table A4

APPENDIX 5: Additional References of Potential Interest

The study designs of the following did not meet the inclusion criteria (systematic review/meta-analysis or randomized controlled trial) for this review and were excluded

1. Moise PA, Culshaw DL, Wong-Beringer A, Bensman J, Lamp KC, Smith WJ, et al. Comparative effectiveness of vancomycin versus daptomycin for MRSA bacteremia with vancomycin MIC >1 mg/L: A multicenter evaluation. *Clin Ther*. 2015 Nov 13. PubMed: PM26585355
2. Usery JB, Vo NH, Finch CK, Cleveland KO, Gelfand MS, Self TH. Evaluation of the treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *Am J Med Sci*. 2015 Jan;349(1):36-41. PubMed: PM25233042
3. Liang SY, Khair HN, McDonald JR, Babcock HM, Marschall J. Daptomycin versus vancomycin for osteoarticular infections due to methicillin-resistant *Staphylococcus aureus* (MRSA): a nested case-control study. *Eur J Clin Microbiol Infect Dis* [Internet]. 2014 Apr [cited 2016 Jan 21];33(4):659-64. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3955410> PubMed: PM24186726
4. Yazdani C, Hanna N. Comparative analysis of empiric antimicrobial treatments for skin and soft tissue infections in newly hospitalized patients. *J Pharm Pract*. 2014 Feb;27(1):53-60. PubMed: PM24076599
5. Szczypinska E, Velazquez A, Salazar D, Deryke CA, Raczynski B, Wallace MR. The impact of initial antibiotic therapy (linezolid, vancomycin, daptomycin) on hospital length of stay for complicated skin and soft tissue infections. *Springerplus* [Internet]. 2013 [cited 2016 Jan 21];2:696. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3884083> PubMed: PM24422184
6. Campbell ML, Marchaim D, Pogue JM, Sunkara B, Bheemreddy S, Bathina P, et al. Treatment of methicillin-resistant *Staphylococcus aureus* infections with a minimal inhibitory concentration of 2 µg/mL to vancomycin: old (trimethoprim/sulfamethoxazole) versus new (daptomycin or linezolid) agents. *Ann Pharmacother*. 2012 Dec;46(12):1587-97. PubMed: PM23212935