Consensus document on controversial issues in the treatment of complicated skin and skin-structure infections

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SUMMARY

Background: Complicated skin and skin-structure infections (cSSSI), including surgical site infections (SSI), cellulitis, and abscesses, have been extensively studied, but controversial issues still exist.
Controversial issues: The aim of this GISIG (Gruppo Italiano di Studio sulle Infezioni Gravi) working group – a panel of multidisciplinary experts – was to define recommendations for the following controversial issues: (1) What is the efficacy of topical negative pressure wound treatment as compared to standard of care in the treatment of severe surgical site infections, i.e., deep infections, caused by Gram-positive microorganisms? (2) Which are the most effective antibiotic therapies in the treatment of cSSSI, including SSI, due to methicillin-resistant staphylococci? Results are presented and discussed.
Methods: A systematic literature search using the MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and www.clinicaltrials.gov databases of randomized controlled trials and/or non-randomized studies was performed. A matrix was created to extract evidence from original studies using the CONSORT method to evaluate randomized clinical trials and the Newcastle–Ottawa Quality Assessment Scale for case–control studies, longitudinal cohorts, and retrospective studies. The GRADE method was used for grading quality of evidence. An analysis of the studies published between 1990 and 2008 is presented and discussed in detail.

1. Introduction

Complicated skin and skin-structure infections (cSSSI), including surgical site infections, cellulites, and abscesses, are common infections, generally caused by Gram-positive cocci, with *Staphylococcus aureus* and streptococci being the most common etiologic agents. In many countries throughout the world, these infections in the hospital setting are due in a worryingly increasing proportion to antibiotic-resistant strains, such as methicillin-resistant *S. aureus* (MRSA).[1] Over the last few years, community-acquired MRSA (CA-MRSA) has become a common problem in North America,[2] while CA-MRSA of pig or cattle origin, also known as livestock-associated MRSA (LA-MRSA), has been identified in

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different countries, including the Netherlands, Italy, and the USA.[3–5] These epidemiological changes are important and should hamper a revision of the literature regarding different aspects of the treatment of cSSSI, with a special interest in surgical site infection (SSI). Different aspects have emerged as interesting in the field of cSSSI, particularly of those caused by MRSA: prevention and antibiotic therapy, as well as non-antibiotic therapy of SSI.

First, the availability of rapid identification systems for *S. aureus*, mostly based upon molecular techniques, now permit the identification of subjects colonized by these germs in a few hours, either methicillin-resistant (MRSA) or methicillin-sensitive (MSSA). The early identification and treatment of these subjects can be both clinically and epidemiologically useful, with the aim of reducing infections in colonized subjects, tailoring antibiotic prophylaxis, and limiting the nosocomial spread of the bacterium.

Second, cSSSI have represented a common setting for the registration of many new antibiotics, including linezolid,[6,7] tigecycline,[8] ceftobiprole,[9] and daptomycin.[10] Most recent comparative studies have evaluated the non-inferiority of a newer drug compared with the standard of care, i.e., a glycopeptide, with costs of the newer drugs being generally much higher than the older ones. A global revision of the results, taking into account the quality of the different studies, to better define the best clinical setting for newer drugs, is needed.

Third, treatment of infected post-surgical wounds may be based upon different strategies, including surgery, antibiotics, dressings, and topical negative pressure (TNP) therapy, defined also as vacuum associated closure (VAC).[5,11–16] TNP/VAC is becoming a standard of care, particularly in the treatment of post-sternotomy infections.[17] Although the system may be effective in treating these infections, the high costs of such an approach and the wide diffusion that TNP/VAC has reached over recent years, particularly in the treatment of post-sternotomy infections, including mediastinitis, make this area of research interesting for a systematic review.

2. Objective

The aim of this study was to review the literature on the optimal treatment of cSSSI, including SSI, caused by resistant Gram-positive strains, with a special focus on studies on newer antibiotics against Gram-positive resistant microorganisms.

3. Methods

3.1. Controversial issues

A group of experts in the field of cSSSI was identified and enrolled in a faculty. The faculty was in charge of defining controversial issues, developing a search strategy, and reviewing the retrieved literature in order to obtain data on controversial issues and to draw recommendations based on the best available evidence.

During two workshop meetings held in Milan, Italy, the group of experts, after discussion within the group, and with the board of the project, identified the following questions to be addressed:

1. "Do topical nasal mupirocin or other local treatments reduce the incidence of surgical site infections?" (decolonization). Regarding this question, a meta-analysis was published by the Cochrane collaboration[18] that covered the same target. Since no relevant paper had been published from May 29, 2008 through February 28, 2009, this analysis was not performed.
2. "What is the efficacy of topical negative pressure wound treatment as compared to the standard of care, in the treatment of severe surgical site infections, i.e., deep, under the fascial and muscle layers, due to Gram-positive microorganisms?" (TNP/VAC).

3. "Which are the most effective therapies in the treatment of complicated skin and skin-structure infections, including surgical site infections?" (cSSSI).

3.2. Literature search and study selection

To these aims, we systematically reviewed comparative studies on the above-mentioned controversial issues on cSSSI. Five different databases were thoroughly searched, namely PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, UK Clinical Research Network Study Portfolio and www.clinicaltrials.gov. In each database the following search terms were used for the two questions:

1. TNP: (a) 'vacuum assisted closure' OR 'VAC' OR 'topical negative pressure' OR 'TNP' OR 'vacuum' AND (b) 'wound' OR 'chronic wound' OR 'ulcer' AND (c) 'infection'.
2. cSSSI: (a) 'skin infection' OR 'soft tissue infection' OR 'surgical wound infection' OR 'surgical site infection' AND (b) 'Gram-positive bacteria' OR 'Staphylococcus' OR 'Staphylococcus aureus' OR MRSA AND (c) 'infection' AND (d) 'randomized controlled trial' (RCT).

A study was considered eligible for analysis if the criteria listed below were met. If data were missing for the programmed analysis in the selected studies, an e-mail requiring data clarification was sent to the corresponding author.
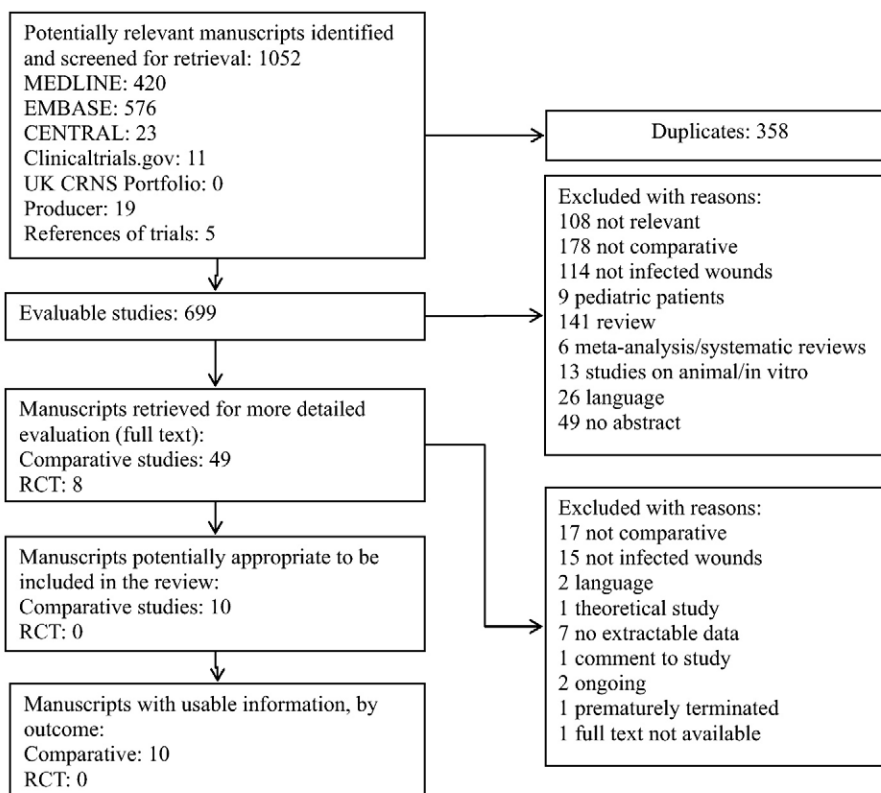
3.3. Question 1 – TNP/VAC

1. Population: any person aged $\geq$13 years who developed a deep surgical site infection. A deep surgical site infection was defined as infection involving the deep soft tissues (e.g., fascial and muscle layers) of the incision, following the Hospital Infection Control Practices Advisory Committee 1999 guideline definition.[19]
2. Intervention: use of any kind of TNP/VAC to treat the infected surgical wound.
3. Control: any type of dressing, including traditional wet gauze dressing and the newer moist dressings, with or without topical agents.
4. Outcome: infection cure/wound resolution, time to complete healing, incidence of complications, duration of hospital stay, incremental costs, quality of life, mortality.
5. Study design: any comparative study either RCT or comparative non-randomized study (CS), either a case–control or a cohort comparative study.

3.4. Question 2 - cSSSI

1. Population: patients aged $\geq$13 years with a diagnosis of complicated skin and skin-structure infection.
2. Intervention: intervention drug, i.e., antibiotic with anti-MRSA activity.
3. Control: comparator, i.e., a second antibiotic or an association of antibiotics, with anti-MRSA activity.
4. Outcome: clinical cure at the test of cure (TOC) visit, so that no further antibiotic or surgery was necessary, microbiological cure at the TOC visit, incidence of adverse events (AEs), duration of intravenous therapy, duration of hospital stay, incremental costs, mortality.
5. Study design: RCT.

The studies were considered eligible if they assessed clinical and/or microbiological effectiveness, toxicity, or mortality of both therapeutic regimens. We included both blinded and unblinded trials as well as any type of statistical design, such as equivalence, non-inferiority, and superiority studies. Only studies written in

Potentially relevant manuscripts identified
and screened for retrieval: 1052
MEDLINE: 420
EMBASE: 576
CENTRAL: 23
Clinicaltrials.gov: 11
UK CRNS Portfolio: 0
Producer: 19
References of trials: 5

→ Duplicates: 358

Excluded with reasons:
108 not relevant
178 not comparative
114 not infected wounds
9 pediatric patients
141 review
6 meta-analysis/systematic reviews
13 studies on animal/in vitro
26 language
49 no abstract

Evaluable studies: 699

Manuscripts retrieved for more detailed
evaluation (full text):
Comparative studies: 49
RCT: 8

Excluded with reasons:
17 not comparative
15 not infected wounds
2 language
1 theoretical study
7 no extractable data
1 comment to study
2 ongoing
1 prematurely terminated
1 full text not available

Manuscripts potentially appropriate to be
included in the review:
Comparative studies: 10
RCT: 0

Manuscripts with usable information, by
outcome:
Comparative: 10
RCT: 0

Legend: CENTRAL = Cochrane Central Register of Controlled Trials; UK CRNS = United
Kingdom Clinical Research Network Study.

Figure 1. Flow diagram of trial selection: use of vacuum-assisted closure (VAC) in infected wounds.

English, French, Italian, or Spanish were included in the analysis. For question 2 (cSSSI), RCTs that did not include any MRSA patient were excluded, as well as those in which one of the study regimens did not have any anti-MRSA activity. Trials focusing on pharmacokinetic or pharmacodynamic variables were also excluded. RCTs that studied additional antimicrobial agents, generally with anti-Gram-negative rods and/or anti-anaerobic activity (as is the case in patients with polymicrobial infections) were included in the analysis.

3.5. Classification and evaluation of the selected evidence

A matrix was made to extract evidence from individual original studies using the CONSORT method for the evaluation of randomized clinical trials and the Newcastle–Ottawa Quality Assessment Scale for the evaluation of case–control trials, longitudinal cohorts, and retrospective studies with comparative groups.[20] The original data from case studies were considered homogeneous after using a predefined format both for single case reports and series of reported cases.[20] In the discussion section, to assign the strength to the level of the recommendations, a methodology adapted from the GRADE Working Group was applied. The details of the methodology are reported in this supplement.[20]

3.6. Definition of infection

3.6.1. Deep surgical site infection

A deep surgical site infection was defined as infection involving the deep soft tissues (e.g., fascial and muscle layers) of the incision, following the Hospital Infection Control Practices Advisory Committee 1999 guideline definition.[19] Complicated skin and skin-structure infections (cSSSI) were defined as infections involving deeper soft tissue and/or requiring significant surgical intervention (e.g., surgical or traumatic wound infection, major abscess, infected ulcer, or deep and extensive cellulitis) or that had developed on a lower extremity in a subject with diabetes mellitus or well-documented peripheral vascular disease. The presence of at least one local sign of cSSSI (i.e., erythema, fluctuance, purulent or seropurulent drainage/discharge, heat/localized warmth, pain/tenderness to palpation, swelling/induration) or one systemic sign (oral temperature of $>38\,°C$, white blood cell count of $>10 \times 10^9/l$, $>10\%$ immature neutrophils) were necessary to define a cSSSI.

4. Results

4.1. Question 1 – TNP/VAC

"What is the efficacy of the topical negative pressure wound treatment as compared to the standard of care, in the treatment of severe surgical site infections, i.e., deep, under the fascial and muscle layers, due to Gram-positive micro-organisms?"

A total of 10 comparative studies were identified (see Figure 1). Of these, six were on post-sternotomy deep surgical site infection, with or without mediastinitis,[21–26] three on post-sternotomy mediastinitis,[27–29] and one on early groin vascular by-pass graft infection[30] (see Tables 1 and 2).

In all studies the main outcome was the cure of the infection or the failure of the therapy. Although the definition of wound cure was not standardized throughout the studies, the definition of wound resolution was based upon the appearance of the wound, the presence of wound granulation and/or resolution of local signs of inflammation, and/or negative cultures in six studies (see Table 2). Two studies referred to a definition of failure, including the need for

Table 1
Data extracted from the comparative studies—I

ID	Aim	Study design	Population	Intervention	Comparator
Berg 2000[21]	Compare the TNP/VAC and closed drainage technique	Retrospective comparative cohort study	Deep surgical site infection of the sternotomy site with positive cultures	Vacuum suction through 3–6 redon catheters (300–600 mmHg); no polyester dressing used	2–4 catheters with CDI (2 l of 0.5% povidone–iodine solution per 24 h continuously)
Catarino 2000[27]	Compare the TNP/VAC and standard therapy	Retrospective comparative cohort study	Patients with early post-sternotomy mediastinitis	TNP/VAC 125 mmHg; changed every 2–3 days	Debridement, CDI with normal saline (1 l every 6 h until the effluent was microbiologically clear)
Colwell 2004[30]	Compare debridement/TNP/VAC vs. incision/drainage + sartorius or rectus femoris muscle flaps	Retrospective comparative cohort study	Patients with early groin vascular by-pass graft infection	TNP/VAC: not specified	Incision and drainage
Fleck 2004[22]	Compare preconditioning of the wound with TNP/VAC with conventional debridement and immediate primary closure	Retrospective comparative cohort study	Patients with post-sternotomy wound infection	TNP/VAC 125 mmHg; changed every 2–3 days	Rewiring and primary wound closure with insertion of a mediastinal drain; daily dressing changes
Fuchs 2005[23]	Compare TNP/VAC with open pack procedure	Retrospective comparative cohort study	Patients with sternotomy and deep surgical wound infection	TNP/VAC 75–125 mmHg; changed every 3–7 days	Irrigation with povidone–iodine, saline and H_2O_2, with wound drainage, open packing and delayed closure
Scholl 2004[24]	Compare TNP/VAC with standard medication as a method to facilitate healing (1) as a temporary wound care technique preoperatively in patients requiring muscle flap reconstruction, (2) as the primary method of wound closure, and (3) in post-reconstructive wounds complicated by re-infection	Retrospective comparative cohort study	Patients with sternotomy and deep surgical wound infection – sternal osteomyelitis	TNP/VAC (continuous or intermittent 25–200 mmHg) + wound debridement; changed every 2 days	Debridement; the type of dressing is not specified
Segers 2005[28]	Compare TNP/VAC with closed drainage techniques	Retrospective comparative cohort study	Post-sternotomy mediastinitis	TNP/VAC 75–125 mmHg; changed after 2 days then every 4–5 days	Debridement followed by closed drainage technique
Simek 2008[25]	Compare clinical outcomes, in-hospital mortality and 1-year survival of topical negative pressure and conventional therapy	Prospective analysis	Deep sternal wound infection	TNP/VAC 125 mmHg; changed every 2–3 days	Debridement followed by chest rewiring and closed irrigation with antiseptics for 6–8 days
Sjögren 2005[29]	Compare the failure rate and survival after single-line TNP/VAC therapy or conventional treatment	Retrospective comparative cohort study	Post-sternotomy mediastinitis	TNP/VAC 125 mmHg; changed ≥3/week	Moist saline gauzes changed several times a day
Song 2003[26]	Compare twice-day gauze with TNP/VAC	Retrospective comparative cohort study	Patients with sternotomy and sternal wound	TNP/VAC 75–125 mmHg; changed every 2 days	Twice-day dressing: debridement; silver sulfadine or mafenide acetate

VAC, vacuum-assisted closure; CDI, continuous drainage irrigation; TNP, topical negative pressure.

Table 2
Data extracted from the comparative studies—II

ID	Outcome 1 Resolution Num/Den (I)	(C)	Outcome 2 Incidence of complications Num/Den (I)	(C)	Outcome 3 Hospital stay Days (mean ± SD) (I)	(C)	Outcome 4 Cost per patient (I)	(C)	Outcome 5 Quality of life (I)	(C)	Outcome 6 Mortality (Time points) Num/Den (I)	(C)	Quality (risk of bias)	Notes
Berg 2000[21]	26/31 [1,2]	14/29	NE	NE	42 ± 26	56 ± 22	NE	NE	NE	NE	2/31 (In-hosp)	2/29	Medium	[1]Failure: re-exploration (debridement, reclosure, a different drainage technique or (muscle) flap reconstruction) of the sternal wound within 60 days after the drainage was applied [2]Variables significantly associated with treatment failure: S. aureus as causative pathogen (p = 0.04), NYHA score (p = 0.04), and severity of mediastinitis (p = 0.02) S. aureus and severity were worse in CDI
Catarino 2000[27]	9/9 [1,2]	5/10	NE	NE	35 (22–88)* (*Median)	50 (27–98)*	NE	NE	NE	NE	1/9 (FU 6 mo)	5/10	Medium	[1]Resolution: evident granulation tissue and negative microbiological cultures (specified only for TNP/VAC) [2]First 2 patients were treated with TNP/VAC 26 and 24 days after diagnosis of infection (initially with CDI)
Colwell 2004[30]	4/4 [1]	4/5 [2]	0/4	1/5	NE	NE	NE	NE	NE	NE	0/4 (FU 2–24 mo)	0/5	Medium	[1]Resolution: no definition [2]In the comparator arm one was debridement+packed wet to dry dressings One reinfection at 4 mo, cured at 2 years Notably: 10–14 days of antibiotic course
Fleck 2004[22]	35/35 [1]	62/97	NE	NE	19 (7–45)* (*Median)	24 (5–72)*	NE	NE	NE	NE	NE [2]	NE	High	[1]Resolution of infection: decline of serological inflammation parameters, less than 100 000 CFU per g of tissue in bacteriological cultures, and resolution of local infection signs in the wound [2]Overall in-hospital mortality: 7%
Fuchs 2005[23]	34/35 [1,2] 21 (IQR 15–26)* (*Time to wound healing)	29/33 28 (18–54)*	NE	NE	25 (18–35)* (*Median)	34 (24–55)*	NE	NE	NE	NE	1/35	8/33	Medium	[1]Resolution: 3 negative sternal wound samples [2]In both study groups, rewiring was done without the use of muscle flaps or omentoplasty
Scholl 2004[24]	6/7 [1]	6/6	1/7	1/6	NE	NE	NE	NE	NE	NE	0/7 [2]	0/6	Medium	[1]Resolution: no definition 5 pre-operative, 1 post-op, 1 pre- and post-op One patient treated with TNP/VAC healed after reoperation 12/13 patients underwent bilateral pectoralis major muscle flaps for reconstruction [2]Mean FU: 14 mo
Segers 2005[28]	21/29 [1]	14/34	1/29	0/34 [2]	46.1 (10–74)* (*Range)	35.7 (10–167)*	NE	NE	NE	NE	1/29 (FU 1 mo) 9/29 (FU 12 mo)	1/34 8/34	Medium	[1]Failure: recurrence of wound infection, a change to other treatment techniques and the need for multiple surgical interventions to control infection or mortality caused primarily by the surgical site infection [2]Not clearly specified

Table 2 (*Continued*)

ID	Outcome 1 Resolution Num/Den		Outcome 2 Incidence of complications Num/Den		Outcome 3 Hospital stay Days (mean ± SD)		Outcome 4 Cost per patient		Outcome 5 Quality of life		Outcome 6 Mortality (Time points) Num/Den		Quality (risk of bias)	Notes
	(I)	(C)	(I)	(C)	(I)	(C)	(I)	(C)	(I)	(C)	(I)	(C)		
Simek 2008[25]	32/34 [1]	17/28	6/34 [2]	4/28	40.2 ± 16.3	48.8 ± 29.2	NE	NE	NE	NE	2/34 (In-hosp) 5/34 (FU 12 mo)	11/28 11/28	Low	[1]Resolution of infection: wound bed was found free of infection, covered by well-vascularized granulation tissue, and the CRP level ≤50 mg/L Treatment failure: not defined [2]Incidence of major bleeding and fistula
Sjögren 2005[29]	61/61 [1]	25/40	4/61 [2]	2/40	25 ± 17	25 ± 20	NE	NE	NE	NE	0/61 (FU 3 mo)	6/40	Medium	[1]Resolution: wound was considered clean and there was a bed of fresh granulation tissue All 61 patients in the TNP/VAC group underwent sternal rewiring without tissue flap surgery. In the conventional treatment group, tissue flaps were performed in 57.5% (23 patients) Results are stratified as per type of mediastinitis (El Oakley class) [2]Fistula
Song 2003[26]	14/17 [1] 6 ± 1.3* (*Time to wound healing)	17/18 8 ± 2.9*	2/14	6/17	NE	NE	NE	NE	NE	NE	3/17 (In-hosp)	1/18	Medium	[1]Resolution: gross appearance of the wound and hemodynamic stability of the patient 28 mediastinitis, 5 chronic infection and 2 sterile wounds Number of flaps needed to close the wound: non-TNP/VAC group = 1.5 ± 0.1, TNP/VAC group = 0.9 ± 0.07 (*p* < 0.05)
Total	242/266	193/300	14/149	14/131			NE	NE	NE	NE	17/132	26/133		

NE, not examined; NYHA, New York Heart Association; CDI, continuous drainage irrigation; mo, months; FU, follow-up; IQR, interquartile range; TNP, topical negative pressure; VAC, vacuum-assisted closure; CRP, C-reactive protein; I, intervention; C, control; Num, numerator; Den, denominator.

Table 3
Evaluation of the quality of the studies based upon the NOS score

	Selection (0–4)				Comparability (0–2)		Outcome (0–3)			Overall quality
	Representativeness	Selection of non-exposed	Ascertainment of exposure	Outcome of interest	Comparability	Control for a second factor	Assess outcome	FU long enough	Adequacy FU cohorts	Risk of bias
Berg 2000[21]	*	*	*	*	*	*	*	0	0	Medium
Catarino 2000[27]	*	*	*	*	*	*	0	*	0	Medium
Colwell 2004[30]	*	*	*	*	*	0	*	0	0	Medium
Fleck 2004[22]	*	*	*	*	0	0	0	0	0	High
Fuchs 2005[23]	*	*	*	*	*	*	0	*	*	Low
Scholl 2004[24]	*	*	*	*	*	0	*	0	0	Medium
Segers 2005[28]	*	*	*	*	0	*	*	0	*	Medium
Simek 2008[25]	*	*	*	*	*	*	0	*	*	Low
Sjögren 2005[29]	*	*	*	*	*	0	0	*	*	Medium
Song 2003[26]	*	*	*	*	*	*	0	0	0	Medium

FU, follow-up; *, item adequately fullfilled.

re-operation.[21,27] In two studies no definition of resolution was reported.[24,30]

4.2. Patient populations

The patient populations were similar between the two study groups throughout most studies, although in one study no data regarding the demographic and general characteristics of the two groups were reported[22] and in another overall data only were available.[24] The mean age was similar between the two treatment groups in all the studies, ranging between 61 and 72.6 years. A significantly higher proportion of females in the TNP/VAC arm was observed in two studies.[28,29] Finally, one study reported a longer duration of intervention[28] and another a higher EUROscore, an index of surgical complexity,[29] and a lower proportion of S. aureus infections[21] in the TNP/VAC arm.

4.3. Intervention

The modalities of TNP/VAC were relatively similar throughout the studies: a negative pressure of 75–125 mmHg was used in seven studies, as was the time interval between dressing changes, i.e. 48–72 h (see Table 1). One study used higher pressures, 300–600 mmHg,[21] another lower pressures (25–200 mmHg).[24] In one study the pressure used was not specified.[30]

4.4. Control

The comparative conventional therapies were continuous drainage irrigation in two studies[21,27] and closed drainage irrigation in five.[22,23,25,28,30]

4.5. Study design

Nine studies were retrospective comparative cohort studies, while a single study was prospective (see Tables 1 and 2).[25] No RCT was retrieved.

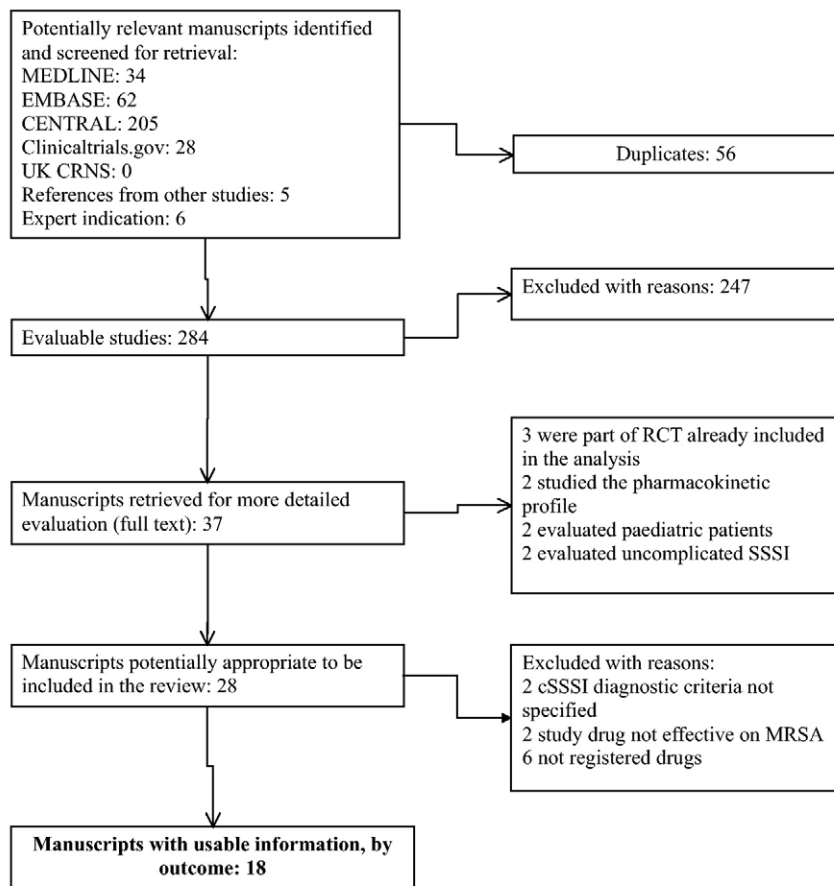### 4.6. Risk of bias of included studies

The comparative studies retrieved generally had a medium risk of bias, as evaluated through the Newcastle–Ottawa Quality Assessment Scale (NOS; see Table 3). Only two studies showed a low risk of bias.[23,25] Notably, while bias on the selection of patients was low in all selected trials, both comparability and outcome were at higher risk of bias.

4.7. Effects of intervention – primary outcomes

Ten studies were selected for analysis. In none of the studies it was possible to identify the effect of either treatment on infections specifically caused by Gram-positive micro-organisms. The analysis of the results was therefore performed on the whole group of patients treated with TNP/VAC or conventional treatment, irrespectively of the etiologic agent. The methodological quality of these studies was analyzed through the GRADE system (see Table 4). Of these studies, three enrolled patients with post-sternotomy mediastinitis, six evaluated patients with post-sternotomy deep infection, and one study analyzed patients with early groin vascular by-pass graft infection (see Table 1). The studies analyzed reported data regarding 562 patients, of which 262 (47%) had been treated with TNP/VAC and 300 (53%) with conventional therapy. Concerning the main outcome, i.e., cure rate, all studies reported the results as the proportion of patients cured; two studies also reported the time to wound healing.[23,26]

4.8. Results

Six studies reported a difference in wound cure in TNP/VAC as compared with conventional therapy.[21,22,25,26,28] Wound resolution was obtained more frequently in patients treated with TNP/VAC (242/262, 92.4%) as compared with patients cured with standard treatment (193/300, 64.3%) (odds ratio (OR) 6.43, 95% confidence interval (CI) 3.81–10.85).

Table 4
Grade score of the studies on topical negative pressure (TNP)

Trial	Design	Quality	Inconsistency	Directness	Attrition	Bias	Association (RR)	Dose/response	Confounders	Total
Berg 2000[21]	2	−1	0	0	−1	−1	0	0	0	−1
Catarino 2000[27]	2	−1	0	0	0	−1	+1	0	0	1
Colwell 2004[30]	2	−1	0	0	0	−1	0	0	0	0
Fleck 2004[22]	2	−1	0	0	0	−1	0	0	0	0
Fuchs 2005[23]	2	0	0	0	0	−1	0	0	0	1
Scholl 2004[24]	2	−1	0	0	0	−1	0	0	0	0
Segers 2005[28]	2	0	0	0	−1	−1	0	0	0	0
Simek 2008[25]	2	0	0	0	0	−1	0	0	0	1
Sjögren 2005[29]	2	−1	0	0	0	−1	0	0	0	0
Song 2003[26]	2	−1	0	0	−1	−1	0	0	0	−1

Figure 2. Flow diagram of trial selection: antibiotic therapy in complicated skin and skin-structure infections (cSSSI) due to Gram-positive cocci/methicillin-resistant *Staphylococcus aureus* (MRSA).

Time to wound healing was analyzed in two studies: it was a median 21 days (interquartile range (IQR) 15–26) in TNP/VAC treated subjects and 28 (IQR 18–54) in controls (p > 0.05) in one study, and mean ± standard deviation of 6 ± 1.3 in TNP/VAC vs. 8 ± 2.9.[23,26]

The incidence of complications was reported in 6/10 studies, for a total of 280 treated patients (see Table 2). None of the studies reported any difference between TNP/VAC and conventional therapy regarding the incidence of complications. A complication was observed in 14/149 (9.4%) patients treated with TNP/VAC and in 14/131 (10.7%) controls, indicating no significant difference among the groups (OR 0.91, 95% CI 0.42–2.01). Notably, among complications in patients treated with TNP/VAC, a ventricular rupture was observed, causing the patient's death.[23]

The duration of hospital stay was analyzed in seven studies (see Table 2). Three studies reported the mean values with the standard deviation,[21,25,29] one the mean and the range of values,[28] two the median with the interquartile variation (IQV),[23,27] and one the median with the range.[22] Four of these studies reported a significant reduction in hospital-stay in patients treated with TNP/VAC as compared with conventional treatment.[21,23,25,27] In none of these studies was a confidence interval reported. No cost-effectiveness analysis or quality of life investigation was performed in any of the retrieved studies.

Finally, mortality rates were available in 9/10 studies (see Table 2). Three studies reported a reduced mortality rate in patients on

TNP/VAC.[23,25,26] Different time points were analyzed in the different studies: two studies presented data regarding in-hospital mortality,[21,26] two studies presented both short-term (either in-hospital or 1 month) and middle-term (i.e., 1 year) mortality,[25,28] and two studies analyzed the 3- and 6-month mortality, respectively[27,29] (see Table 2). In three cases the time-point of the mortality rate was not clearly specified. The overall mortality rate, i.e., mortality at the last follow-up specified, was 9.3% (21/225) in patients treated with TNP/VAC, while this was 21.2% (41/203) in standard treatment patients (OR 0.44, 95% CI 0.25–0.77). A reduced short term mortality rate, i.e. in-hospital to 6 months, was observed in TNP/VAC-treated subjects: 8/172 (4.7%) as compared to 21/149 (14.1%) in the conventionally treated subjects (OR 0.32, 95% CI 0.14–0.71). Middle-term mortality rates, i.e., mortality at 6–12 months, were similar for the two treatment strategies: 15/70 (21.4%) in the TNP/VAC group and 24/72 (33.3%) in the standard treatment group (OR 0.56, 95% CI 0.27–1.17).

4.9. Question 2 – cSSSI

"Which are the most effective therapies in the treatment of complicated skin and skin-structure infections, including surgical site infections?"

A total of 25 unique studies were identified (see Figure 2).[6–10,31–53] All of the studies retrieved were RCTs (see Tables 5 and 6). Four studies were excluded for different reasons (one study drug

Table 5
Overall data: general characteristics of the selected studies—I

Study ID			Aim	Study design	
Author	Year of pub	Journal			
Noel[9]	2008	AAC	Compare the safety and efficacy of ceftobiprole to those of vancomycin + ceftazidime, in patients with cSSSI	Non-inferiority	Double-blind
Noel[31]	2008	CID	Compare the safety and efficacy of ceftobiprole to those of vancomycin, for the treatment of skin infections due to Gram-positive bacteria in which methicillin resistance is a concern	Non-inferiority	Double-blind
Arbeit[10]	2004	CID	Compare the safety and efficacy of daptomycin with that of conventional therapy (penicillinase-resistant penicillin (PRP) and vancomycin) for the treatment of patients with cSSSI requiring hospitalization	Non-inferiority	Evaluator blinded
Cepeda[32]	2004	JAC	Compare linezolid with teicoplanin in the treatment of Gram-positive infections in critically-ill patients	Superiority	Double-blind
Kohno[33]	2007	JAC	Evaluate the efficacy and safety of linezolid for the treatment of Japanese patients with nosocomial MRSA infections. Vancomycin was chosen as the comparator	Descriptive	Open-label
Lin[34]	2008	IJAA	Compare the clinical efficacy, safety, and tolerability of linezolid with those of vancomycin for the treatment of patients with known or suspected Gram-positive infections and a clinical diagnosis of pneumonia or cSSTI	Descriptive	Double-blind
Lipsky[35]	2004	CID	Compare the efficacy and safety of intravenous and oral formulations of linezolid with that of aminopenicillin/β-lactamase inhibitors (plus vancomycin, if needed for MRSA) for treatment of patients with various types of diabetic foot infection	Equivalence	Open-label
Weigelt[6]	2005	AAC	Compare clinical efficacy, safety, and tolerability of linezolid and vancomycin in the treatment of patients with suspected or proven methicillin-resistant, Gram-positive cSSTIs requiring hospitalization	Superiority	Open-label
Itani[36]	2005	IJAA	Sub-study of Weigelt 2005		
Sharpe[37]	2005	AJS	Not clearly specified. The study reports a comparison the efficacy of linezolid with that of vancomycin	Descriptive	Open-label
Stevens[7]	2002	CID	Compare the safety and efficacy of linezolid with that of vancomycin in treating patients with presumed MRSA infections	Equivalence	Open-label
Li[38]	2001	Pharmacother	Sub-study of Stevens 2002		
Wilcox[39]	2004	JAC	Compare linezolid and teicoplanin in the treatment of suspected or proven Gram-positive infections	Equivalence	Open-label
Nichols[40]	1999	JAC	Compare efficacy, tolerance, and safety of quinupristin–dalfopristin and standard therapy in patients with cSSSI caused by Gram-positive bacteria	Equivalence	Open-label
Breedt[41]	2005	AAC	Determine the efficacy and safety of tigecycline monotherapy and the combination of vancomycin and aztreonam (V/A) and compare the non-inferiority of tigecycline to V/A in hospitalized patients with skin and skin-structure infections	Non-inferiority	Double-blind
Ellis-Grosse[42]	2005	CID	Determine the efficacy and safety of tigecycline monotherapy and the combination of vancomycin and aztreonam in hospitalized patients with skin and skin-structure infections	Non-inferiority	Double-blind
Florescu[43]	2008	JAC	Evaluate the safety and the clinical efficacy of tigecycline in patients with selected serious infections caused by VRE and MRSA. An active control arm was used to interpret the results	Favorable response	Double-blind
Sacchidanand[44]	2005	IJID	Compare safety and efficacy of tigecycline vs. vancomycin + aztreonam in patients with cSSSI	Non-inferiority	Double-blind

AAC, Antimicrob Agents Chemother; CID, Clin Infect Dis; JAC, J Antimicrob Chemother; IJAA, Int J Antimicrob Agents; AJS, American Journal of Surgery; Pharmacother, Pharmacotherapy; IJID, Int J Infect Dis; cSSSI, complicated skin and skin-structure infection; cSSTI, complicated skin and soft tissue infection; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant enterococci.

Table 6
Overall data: general characteristics of the selected studies—II

Study ID	Enrolled patients	Study drug	Comparator	Additional antibiotics allowed	Duration of therapy (days)	Study design	
Noel 2008[9]	784	Ceftobiprole	Vancomycin	Aztreonam, metronidazole	7–14	Non-inferiority	Double-blind
Noel 2008[31]	828	Ceftobiprole	Vancomycin + ceftazidime	Metronidazole	7–14	Non-inferiority	Double-blind
Arbeit 2004[10]	1092	Daptomycin	Vancomycin/PRP	Aztreonam, metronidazole	7–14	Non-inferiority	Evaluator blinded
Cepeda 2004[32]	204[a]	Linezolid	Teicoplanin	Various antibiotics allowed	3–28	Superiority	Double-blind
Kohno 2007[33]	154[a]	Linezolid	Vancomycin	Aztreonam, gentamicin or other anti-Gram-negative	7–21	Descriptive	Open-label
Lin 2008[34]	140[a]	Linezolid	Vancomycin	Aztreonam	7–21	Descriptive	Double-blind
Lipsky 2004[35]	371	Linezolid	Ampicillin–sulbactam or amoxicillin–clavulanic acid	Vancomycin, aztreonam	7–28	Equivalence	Open-label
Weigelt 2005[6]	1200	Linezolid	Vancomycin	Aztreonam or other anti-Gram-negative	7–14	Superiority	Open-label
Itani 2005[36]	(Sub-study)						
Sharpe 2005[37]	117	Linezolid	Vancomycin	Any antibiotic not effective against MRSA for two RCTs	7–21	Descriptive	Open-label
Stevens 2002[7]	460[a]	Linezolid	Vancomycin	Aztreonam, gentamicin	7–14	Equivalence	Open-label
Li 2001[38]	(Sub-study)						
Wilcox 2004[39]	438[a]	Linezolid	Teicoplanin	Aztreonam, gentamicin, amikacin, ciprofloxacin, ceftazidime, imipenem, metronidazole	7–28	Equivalence	Open-label
Nichols 1999[40]	893	Quinupristin–dalfopristin	Vancomycin/cefazolin/oxacillin	Aztreonam	3–14	Equivalence	Open-label
Breedt 2005[41]	546	Tigecycline	Vancomycin + aztreonam	No	Up to 14	Non-inferiority	Double-blind
Ellis-Grosse 2005[42]	1129	Tigecycline	Vancomycin + aztreonam	No	Up to 14	Non-inferiority	Double-blind
Florescu 2008[43]	172	Tigecycline	Vancomycin/ linezolid	Anti-Gram-negative antibiotics	7–28	Favorable response	Double-blind
Sacchidanand 2005[44]	573	Tigecycline	Vancomycin + aztreonam	No	Up to 14	Non-inferiority	Double-blind

PRP, penicillinase-resistant penicillin; MRSA, methicillin-resistant *Staphylococcus aureus*.
[a] The study enrolled also patients with other types of infection.

was not effective against MRSA for two,[52,53] no data were reported regarding the diagnostic criteria of cSSSI for two others[50,51]) and six studies were excluded after panel discussion, since they focused on drugs not yet registered, i.e., ceftaroline,[45] dalbavancin,[46,47] and telavancin.[48–50] Of the 18 studies from which data were extracted, two reported pharmaco-economical data of two studies included in the analysis.[36,38] All the selected studies were published from 1999 onwards.

4.10. Patient populations

All studies evaluated both male and female adults; one study also enrolled patients of ≥13 years of age,[39] and a second one enrolled patients ≥16 years of age.[32] The mean age of the enrolled populations ranged from 41.6 to 76 years. In all of the studies the majority of patients were male, with the proportion ranging from 54% to 71%.[35,39]

Table 7
Patients enrolled in the study and treated as per intention to treat (ITT), clinically and microbiologically evaluable at test of cure (TOC)

Author	Drugs		ITT				Clinically evaluable				Microbiologically evaluable			
			Study drug		Comparator		Study drug		Comparator		Study drug		Comparator	
	Study drug	Study drug	Cure	Total	Cure	Total	Cure	Total	Cure	Total	Cure	Total	Cure	Total
Noel 2008[9]	Ceftobiprole	Vancomycin	309	397	300	387	263	282	259	277	NR	NR	NR	NR
Noel 2008[31]	Ceftobiprole	Vancomycin + ceftazidime	448	547	227	281	292	318	149	165	NR	NR	NR	NR
Arbeit 2004[10]	Daptomycin	Vancomycin/ PRP	382	534	397	558	372	446	384	456	21	28	25	36
Kohno 2007[33]	Linezolid	Vancomycin	NR	NR	NR	NR	NR	NR	NR	NR	13	18	4	10
Lin 2008[34]	Linezolid	Vancomycin	31	33	19	29	30	33	19	24	NR	NR	NR	NR
Lipsky 2004[35]	Linezolid	PRP (+ vancomycin)	165	241	77	120	NR	NR	NR	NR	NR	NR	NR	NR
Weigelt 2005[6]	Linezolid	Vancomycin	439	592	402	588	436	462	394	436	NR	NR	NR	NR
Sharpe 2005[37]	Linezolid	Vancomycin	NR	NR	NR	NR	29	30	13	30	29	30	23	30
Stevens 2002[7]	Linezolid	Vancomycin	64	122	54	108	64	99	54	87	27	30	22	30
Wilcox 2004[39]	Linezolid	Teicoplanin	113	123	103	117	99	106	89	102	23	32	10	18
Cepeda 2004[32]	Linezolid	Teicoplanin	23	32	10	18	23	32	10	15	7	9	3	6
Nichols 1999[40]	Quinupristin–dalfopristin	Vancomycin/ cefazolin/ oxacillin	197	450	193	443	197	289	193	273	5	6	3	6
Breedt 2005[41]	Tigecycline	Vancomycin + aztreonam	220	274	225	269	200	223	201	213	25	32	25	33
Ellis-Grosse 2005[42]	Tigecycline	Vancomycin + aztreonam	365	556	364	550	365	422	364	411	NR	NR	NR	NR
Florescu 2008[43]	Tigecycline	Vancomycin/ linezolid	55	81	20	23	NR	NR	NR	NR	NR	NR	NR	NR
Sacchidanand 2005[44]	Tigecycline	Vancomycin + aztreonam	165	292	163	281	165	199	163	198	16	21	17	21

NR, not reported.

Table 8
Overall data: study design and quality score, calculated using the Jadad modified method

Study ID	Study design	Random	Validity of randomization	Double-blind	Validity of double-blind	Withdrawal and/or dropouts	Total	Quality
Noel 2008[9]	Double-blind	1	1	1	0	1	4	High
Noel 2008[31]	Double-blind	1	0	1	0	0	2	Low
Arbeit 2004[10]	Evaluator blinded	1	0	0	0	1	2	Low
Lin 2008[34]	Double-blind	1	0	0	0	1	2	Low
Lipsky 2004[35]	Open-label	1	0	NA	NA	0	1	Low
Itani 2005[36]	Open-label	1	0	NA	NA	1	2	Low
Weigelt 2005[6]	(Sub-study)							
Kohno 2007[33]	Open-label	1	0	NA	NA	1	2	Low
Sharpe 2005[37]	Open-label	1	0	NA	NA	0	1	Low
Stevens 2002[7]	Open-label	1	0	NA	NA	1	2	Low
Li 2001[38]	(Sub-study)							
Wilcox 2004[39]	Open-label	1	1	NA	NA	1	3	High
Cepeda 2004[32]	Double-blind	1	1	1	1	1	5	High
Nichols 1999[40]	Open-label	1	1	NA	NA	0	2	Low
Breedt 2005[41]	Double-blind	1	0	0	0	1	2	Low
Ellis-Grosse 2005[42]	Double-blind	1	0	0	1	1	3	High
Florescu 2008[43]	Double-blind	1	1	1	1	1	5	High
Sacchidanand 2005[44]	Double-blind	1	1	1	0	1	4	High

NA, not applicable.

Table 9
Quality assessment of trials comparing the efficacy of different antibiotics in the treatment of complicated skin and skin-structure infections, following the GRADE recommendations

Study ID	Design	Quality	Inconsistency	Directness	Attrition	Bias	Association (RR)	Dose/response	Confounders	Total
Noel 2008[9]	4	0	0	0	−1	0	0	0	0	3
Noel 2008[31]	4	−1	0	0	0	0	0	0	0	3
Arbeit 2004[10]	4	−2	0	0	0	0	0	0	0	2
Lin 2008[34]	4	−2	0	0	0	0	0	0	0	2
Lipsky 2004[35]	4	−2	0	0	0	−1	0	0	0	1
Weigelt 2005[6]	4	−2	0	0	0	0	0	0	0	2
Kohno 2007[33]	4	−2	0	0	−1	0	0	0	0	1
Sharpe 2005[37]	4	−2	0	0	−1	−1	0	0	0	2
Stevens 2002[7]	4	−2	0	0	−1	0	0	0	0	1
Li 2001[38]	4	−2	0	0	−1	0	0	0	0	1
Wilcox 2004[39]	4	−1	0	0	0	0	0	0	0	3
Cepeda 2004[32]	4	0	0	0	0	0	0	0	0	4
Nichols 1999[40]	4	−1	0	0	−1	−1	0	0	0	1
Breedt 2005[41]	4	−2	0	0	0	0	0	0	0	2
Ellis-Grosse 2005[42]	4	−1	0	0	0	0	0	0	0	3
Florescu 2008[43]	4	0	0	0	0	0	0	0	0	4
Sacchidanand 2005[44]	4	0	0	0	0	0	0	0	0	4

4.11. Interventions

The interventions evaluated in the studies identified are represented by an antibiotic monotherapy compared with another monotherapy or with a combination of two antibiotics (see Table 6). The antibiotics studied were represented by: ceftobiprole,[9,32] daptomycin,[10] linezolid,[6,7,32–49] quinupristin/dalfopristin,[40] and tigecycline.[41–44] The comparators are reported in Table 6.

4.12. Outcomes

The primary outcome of clinical cure of cSSSI was reported in 14/16 studies on the overall population (see Table 7). Data regarding clinical cure in MSSA infections could be retrieved in five studies, data on MRSA in eight studies, while data on streptococcal infections were reported in eight papers. No study reported clinical data regarding enterococcal infections.

A microbiological analysis was reported in 9/16 studies. Data regarding microbiological success for the different germs were reported as follows: MSSA: eight studies; MRSA: nine; enterococci: six; streptococci: eight.

AEs were reported in all but one study,[37] while another study reported only partial data.[33] Data regarding mortality were available in 12 studies, while they were not retrievable for patients with cSSSI in four studies.[7,34,39,43]

Pharmaco-economic data were also retrieved: the duration of hospital stay was reported in three papers, and the length of intravenous therapy and the total duration of therapy were reported in 12 and five studies, respectively.

4.13. Risk of bias in included studies

Forty percent of the RCTs analyzed had a low risk of bias (6/15), while the remaining studies had a high risk of bias, based upon the modified Jadad score as reported in Table 8.[19] This scoring system is based upon an evaluation of five parameters: randomization, double-blinding, dropouts and withdrawals, generation of random numbers, and allocation concealment. For each of these parameters, if they were specified following the Jadad criteria, a point was given.

The attrition, i.e., the number of the initially randomized patients that were not clinically evaluable, was similar among the two study arms in all studies, in most papers below 25%, varying from about 10%[31,35] to over 45%.[37]

4.14. Global overview

A total of 8278 patients were enrolled in the 16 studies analyzed; of these, 8158 (98.6%) were randomized to receive either the intervention drug (patient group, n = 4335) or the comparator(s) (n = 3823). An infection due to MRSA was diagnosed in 1698/

8278 (20.5%) of the enrolled patients. The other Gram-positive organisms commonly reported were: MSSA (2309 patients, 27.9%), streptococci (918 patients, 11.1%), and enterococci (236 patients, 2.9%).

4.15. Effects of intervention – primary outcomes

The methodological quality of the studies was analyzed through the GRADE system (see Table 9). Data regarding treatment success for intention to treat (ITT) at TOC visit were available for 13 of the 16 studies, while data regarding clinical efficacy at TOC visit were retrievable from 10 papers (see Table 7). In most RCTs the comparison was performed between the intervention drug and vancomycin or, less frequently, teicoplanin. In one case, the study compared linezolid with a combination of penicillin and a β-lactamase inhibitor (PBLI).[35]

The overall efficacy was similar for study drugs and comparators in most studies. A significant difference was observed in three studies, all of them comparing linezolid with vancomycin.[6,35,38] A trend towards a significant difference was observed in a further study comparing linezolid with PBLI/vancomycin.[35]

When the subset of patients with a microbiological diagnosis of MRSA infection was analyzed, some studies reported data on clinical efficacy only,[6,9,31,35] some on microbiology efficacy only,[10,32,33,40,42,44] and three on both.[7,33,41] Two studies only observed a significant difference, either clinical[6] or microbiological:[37] in both cases linezolid was superior to vancomycin. Of note, the absolute number of MRSA patients evaluated in tigecycline studies[41,43] was very small, i.e., 93.

Data regarding mortality were reported in 12 studies. The studies that included only patients with cSSSI reported very low mortality rates, varying between 0% and 1.5%. No difference was observed throughout the comparisons.

The incidence of AEs, was reported in 14/16 studies. Notably, only one study,[9] reported the World Health Organization (WHO) grading system of AE, with serious AE having WHO grade >3. Three study drugs showed a higher incidence of AE than the comparator: linezolid, quinupristin/dalfopristin, and tigecycline. The studies comparing linezolid with a glycopeptide/PBLI showed a significantly lower proportion of AE in the control group (36.8% vs. 42.6% for glycopeptide/PBLI and linezolid, respectively). This difference persisted even if the patients included in the study by Lipsky et al.,[35] based upon PBLI, were not considered (OR 1.23, 95% CI 1.03–1.48). In these studies the most common AEs in the linezolid group were represented by diarrhea, nausea, anemia, thrombocytopenia, and liver disease, while the glycopeptide-treated group presented more frequently renal failure and rash. Quinupristin/dalfopristin was associated with a significantly higher proportion of AEs than vancomycin/penicillinase-resistant penicillin (PRP): 62.9% vs. 54%, mainly gastrointestinal problems and venous events. Finally, tigecycline was associated with a higher incidence of AE than vancomycin plus aztreonam: 67.8% vs. 61.3%, the most common AE for tigecycline being gastrointestinal symptoms, such as nausea (over a third of the patients) and vomiting, while patients on vancomycin/aztreonam complained more frequently of skin problems and abnormal liver function tests.

Serious AEs (SAEs) were reported in detail in 14 studies, while one study[47] reported only the total number of SAEs in the whole study population. No difference was observed between any study arm.

4.16. Secondary outcomes

Microbiological cure was reported in nine of the 16 studies (see Table 7). No significant difference was reported between the intervention drug and the comparator in all but one comparison

(linezolid) that determined a significantly better microbiological eradication than the comparators (OR 2.17, 95% CI 1.38–3.42).

The duration of intravenous therapy was reported by 12 studies.[9,10,31,34,35,37–40,42,44,45] In seven of these studies, one comparing daptomycin with vancomycin/PRP,[10] five linezolid vs. glycopeptide/PRP,[35–39] and one quinupristin/dalfopristin,[40] the intervention arm showed a shorter duration of intravenous therapy.

The duration of hospital stay was analyzed in three studies, all of them comparing linezolid with vancomycin. In two of these three studies, a shorter duration of hospital stay was observed. Notably, two studies, one by Itani and colleagues[36] and the other by Li and colleagues,[38] specifically addressed pharmaco-economic issues, and one single study[37] compared the cost of linezolid treatment with that of standard therapy, i.e., vancomycin. The authors calculated a significant saving of money when the patients were treated with linezolid.

5. From the evidence to the recommendations

5.1. Question 1

"What is the efficacy of topical negative pressure wound treatment as compared to the standard of care, in the treatment of severe surgical site infections, i.e., deep, under the fascial and muscle layers, due to Gram-positive microorganisms?"

5.2. Discussion

The application of negative pressure to favor wound healing was introduced into clinical practice in the 1960s, but was standardized with the introduction of TNP/VAC in the 1990s.[54] The possibility of maintaining a closed and clean environment, and the continuous drainage of necrotic and bacterial debris, could theoretically improve the time taken to wound cure.[54] Due to the limitation of alternative effective therapies, and to the experience of some centers, TNP/VAC has become, in many hospitals, the standard of care for difficult to treat chronic wounds, including post-sternotomy mediastinitis, despite the fact that its efficacy and complications in this setting have not been fully investigated.[17]

We analyzed 699 papers, and did not find a single RCT that addressed the problem. A multicenter European trial on TNP/VAC treatment of post-sternotomy mediastinitis has recently been prematurely terminated due to a lack of patient enrolment.[55] We identified 10 comparative studies that satisfied all inclusion criteria, with an overall medium risk of bias, that enrolled a total of 562 patients (see Tables 1 and 2).[21–30] It was not possible to identify, within the selected studies, the clinical outcome of infections stratified by Gram-positive or Gram-negative pathogens. The overall analysis performed showed that TNP/VAC was significantly more effective in 6/10 studies than standard therapy in the cure of post-sternotomy mediastinitis and of deep sternal wound infections, which, to date, represent the major indications of this therapeutic approach in the setting of an infection. Time to wound healing was reported in two of the 10 studies[23,26] and no significant difference was observed between the two treatments. No increased risk of complication was observed among TNP/VAC-treated patients, although one patient died of ventricular rupture due to TNP/VAC.

Both short-term (in-hospital to 3 months) and last follow-up visit mortality rates were significantly lower in TNP/VAC-treated patients than in the standard care patients, while middle-term mortality (6–12 months) was similar in the two groups.

Patients treated with TNP/VAC had a shorter duration of hospital stay. No study compared the cost of TNP/VAC and

standard therapy, nor did any study address the quality of life issues.

There are several limitations to the interpretation of these results. First of all, the overall quality of the studies is generally low, with no available well-designed RCTs. The studies analyzed generally show a medium risk of bias. Only in three cases did a study have a GRADE score ≥1 (see Table 4).[23,25,27] In five cases the GRADE score was zero,[22,24,28–30] while in the remaining two studies it was −1.[21,29] However, when only the three higher quality studies were analyzed, the overall results were confirmed: a significant difference in the effect of TNP/VAC vs. standard therapy was still observed (OR 9.19, 95% CI 2.77–30.48). These three studies did not show any significant difference in mortality between the two treatment strategies (OR 0.56, 95% CI 0.27–1.17).

Second, the TNP/VAC was not well standardized among the studies: it was used at different pressures and the foam was changed at different time intervals. Third, the debridement and drainage procedures used as comparator varied significantly between and among centers. Fourth, in patients with post-sternotomy mediastinitis and deep surgical site infection, antibiotic treatment is mandatory and should preferably be prescribed by an infectious disease consultant. Unfortunately, no specific information was reported in any study regarding the antibiotic treatment, i.e., molecule, dose, duration. Finally this limited amount of comparative data is restricted almost exclusively to one single type of infection: post-sternotomy infections.

Recommendations

The use of TNP/VAC in patients with a post-sternotomy infection, either mediastinitis or deep surgical site infection, is a possible alternative to the standard therapy (grade D). The cost-effectiveness of TNP/VAC should be carefully evaluated.

In the treatment of infected wounds TNP/VAC should be reserved only for patients with post-sternotomy infections, including mediastinitis (grade D).

A standardized protocol, both for the use of TNP/VAC and for the standard care of the infected wound should be defined in each cardiac and thoracic surgery department to reduce intra-hospital variability (grade D).

5.3. Question 2

"Which are the most effective therapies in the treatment of complicated skin and skin-structure infections, including surgical site infections?"

5.4. Discussion

Complicated skin and skin-structure infections are caused by Gram-positive cocci in the majority of cases.[1] Treatment of cSSSI has been, over the years, an area of intense investigation that has permitted the registration of most of the novel antibiotics, particularly of those active against MRSA, such as linezolid, tigecycline, and daptomycin. With the new epidemiological situation, characterized by a dramatic increase in the proportion of CA-MRSA in North America[1] and by the emergence of LA-MRSA in Europe,[3] with both germs frequently causing cSSSI, there is a need to better define the potency and tolerability of the different drugs indicated in the treatment of these infections.

The analysis of the literature identified seven different registered anti-MRSA drugs for which RCTs have been published since 1990. In most cases the performed studies evaluated the efficacy of a novel drug as compared to the standard of care, represented in most cases by a glycopeptide, generally vancomy-

cin and, less frequently, teicoplanin, or in a single study, by PBLI (see Table 6). Notably, as in other areas of pharmacological research, most studies aimed to demonstrate a non-inferiority of the newer drug as compared to the older: in the 18 studies that we analyzed, there were only two superiority studies. Due to the high costs of clinical research, we think that systematic reviews and meta-analyses will represent an important tool in the future to better define which are the most potent and better tolerated drugs.

We applied a methodology adapted from the GRADE Working Group to assign a strength level to the recommendations. The GRADE score of the studies analyzed was high (GRADE 4) in three of 18 studies (17%).[32,43,44] Four studies (22%) were of medium quality (GRADE 3)[9,31,39,42] and the majority, i.e., the remaining 11 studies (61%) were of low quality (GRADE ≤2).

Comparisons between these different drugs allowed the verification that ceftobiprole, daptomycin, quinupristin/dalfopristin, and tigecycline are as effective as vancomycin when evaluating the clinical efficacy for ITT analysis. The only comparison that permitted the identification of a significant difference between the study drugs was linezolid vs. glycopeptide/PBLI, where linezolid performed better than the comparator in three out of seven studies. When the analysis was performed on the population of patients with confirmed MRSA infections, the superiority of linezolid vs. glycopeptide/PRP was observed in two of six studies. No other difference was observed for any other drug. No difference in mortality was observed in any comparison, as was expected due to the low overall mortality of cSSSI.

The analysis on AEs yielded interesting results. The incidence of SAEs was similar throughout all comparisons. The global incidence of AEs was similar between the new cephalosporin and vancomycin/PRP, as well as between daptomycin and vancomycin/PRP. All the other newer drugs, i.e., linezolid, quinupristin/dalfopristin, and tigecycline, were tolerated significantly worse than the glycopeptides. It is interesting to point out that vancomycin is generally considered a relatively toxic and not well tolerated drug.

Data regarding duration of hospital stay were available only for three studies, all evaluating linezolid, and showing a reduced duration of hospital stay in patients treated with this drug. Furthermore, the majority of studies reported the duration of intravenous therapy, showing a significantly shorter duration of intravenous therapy consistently reported in patients treated with linezolid as compared with vancomycin/PRP. A shorter duration of intravenous therapy was also reported in two studies comparing daptomycin and quinupristin/dalfopristin with vancomycin/PRP. One single study evaluated the costs associated with linezolid vs. vancomycin in MRSA-infected patients, with a significant advantage for linezolid. Data regarding the pharmaco-economic issue are in favor of linezolid, to-date the only oral drug with anti-MRSA activity among the newer antibiotics. Since the newer drugs have costs that are consistently higher than vancomycin, the economic analysis plays an important role in the choice of the antibiotic to be used. No pharmaco-economic analysis was found specifically addressing cSSSI, performed within an RCT.

Among the limitations to this analysis, the most important is that most of the RCTs evaluating linezolid were open-label, thus of reduced quality as compared with the double-blind study design. The quality score applying the modified Jadad methodology[19] of the studies evaluating linezolid was generally low to medium (see Table 9). Similarly, a low GRADE score was observed in most studies. One single small study, evaluating 60 patients, reported a cost-effectiveness analysis.[37] No study was found that made a comparison with the efficacy of older drugs with at least a partial anti-MRSA activity, such as tetracycline, clindamycin, co-trimoxazole, and fusidic acid. RCTs have been performed with some of these drugs in uncomplicated skin and soft tissue infections,

although, in our opinion, further investigation is needed, due also to the availability of oral formulations for some of these drugs.

Interestingly, in most studies analyzed, therapeutic drug monitoring of vancomycin was not a part of the study protocol, being left to the decision of the investigator. This lack of vancomycin therapeutic dose monitoring could have led to both increased toxicity due to high trough levels, as well as reduced efficacy due to low concentrations.

Finally, the studies analyzed did not enroll patients with severe disease, such as necrotizing fasciitis, gangrene, and ecthyma gangrenosum, thus limiting the utility of the results, although some papers did include patients with positive blood stream infections.

Recommendations

Glycopeptides (vancomycin and teicoplanin) should be considered as the standard of care in patients with cSSSI due to MRSA (grade A).

Linezolid appears to be more effective than glycopeptides (grade C). Linezolid could be an alternative treatment to glycopeptides despite the low to medium methodological quality of analyzed trials (grade D).

Newer drugs, tigecycline (grade B) and daptomycin (grade C), are as effective as glycopeptides.

When choosing the therapeutic strategy, the pharmaco-economic issue should be considered, i.e., cost of the drug, duration of intravenous therapy, length of hospital stay, and early discharge; a switch to the oral drug should be made whenever possible (grade C).

Always carefully consider the pharmacokinetic and pharmacodynamic parameters of chosen drugs. Monitor glycopeptide trough levels and adapt their dosage according to the available guidelines (grade D).

Conflict of interest

All members of the faculty of GISIG – G. Carosi, R. Cauda, E. Concia, S. Esposito, G. Ippolito, F.N. Lauria, M. Moroni, E. Nicastri, A. Pan, G. Sganga, S. Stefani – report no other potential conflict of interest except as reported in the specific section.

The members of the working group have no specific conflict of interest to report.

Additional Conflict of interest

Conflict of interest for R. Cauda: GlaxoSmithKline, Gilead, Bristol Myers Squibb, Boehringer Ingelheim, Pfizer, Abbott, Merck Sharp & Dohme, Wyeth. Funding received from GlaxoSmithKline, Gilead, Bristol Myers Squibb, Boehringer Ingelheim, Pfizer, Abbott, Merck Sharp & Dohme. S. Esposito has received fees for speaking at national and international meetings and for consulting on Advisory boards from Pfizer, Novartis farma and Wyeth Lederle. G. Sganga has received honoraria for speaking for Pfizer. G. Ippolito and F.N. Lauria have received expert opinion fees from Pfizer. E. Nicastri has received paid expert opinion from MSD and Pfizer. A. Pan has received paid expert opinion fees from Janssen.

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