Conceptrichtlijn Preventie van postoperatieve wondinfecties

INITIATIEF
Nederlandse Vereniging voor Heelkunde

IN SAMENWERKING MET
Nederlandse Vereniging voor Medische Microbiologie
Nederlandse Orthopaedische Vereniging
Nederlandse Vereniging voor Thoraxchirurgie
Nederlandse Vereniging voor Neurochirurgie
Nederlandse Vereniging voor Plastische Chirurgie
Nederlandse vereniging voor Anesthesiologie
Nederlandse Vereniging voor Obstetrie en Gynaecologie
Nederlandse Vereniging voor KNO-heelkunde en heelkunde hoofd-halsgebied
Nederlands Oogheelkundig Gezelschap
Nederlandse Vereniging voor Urologie
Nederlandse Vereniging voor Anesthesiemedewerkers Landelijke Vereniging van Operatieassistenten
Nederlandse Vereniging van Leidinggevenden OK
Vereniging voor Hygiëne & Infectiepreventie in de Gezondheidszorg

MET ONDERSTEUNING VAN
Kennisinstituut van de Federatie Medisch Specialisten

FINANCIERING
De richtlijnontwikkeling werd gefinancierd uit [de Stichting Kwaliteitsgelden Medisch Specialisten (SKMS) of andere bron].

Colofon

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Samenstelling van de werkgroep

Werkgroep

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- Mw. drs. H. (Hannah) Groenen, arts-onderzoeker, Nederlandse Vereniging voor Heelkunde
- Dhr. dr. M.J. (Maarten) van der Laan, vaatchirurg, Nederlandse Vereniging voor Heelkund
- Dhr. dr. F.F.A. (Frank) Ijpma, Traumachirurg, Nederlandse Vereniging voor Traumachirurgie
- Dhr. dr. W.C. (Wil) van der Zwet, Arts-microbioloog, Nederlandse Vereniging voor Medische Microbiologie
- Dhr. dr. P. (Patrique) Segers, cardiothoracaal chirurg, Nederlandse Vereniging voor Thoraxchirurgie
- Dhr. dr. D.R. (Dennis) Buis, neurochirurg, Nederlandse Vereniging voor Neurochirurgie
- Mw. Y.E.M. (Yasmine) Dreissen, AIOS neurochirurgie, Nederlandse Vereniging voor Neurochirurgie
- Dhr. R.R. (Roald) Schaad, anesthesioloog, Nederlandse Vereniging voor Anesthesiologie
- Dhr. dr. J.H.M. (Jon) Goosen, orthopaedisch chirurg, Nederlandse Orthopaedische Vereniging

Meelezers

- Dhr. drs. R.O.B. de Keizer, oogarts, Nederlands Oogheelkundig Gezelschap.
- Dhr. drs. W.A. (Willem) Dijckmeester, KNO-arts, Nederlandse Vereniging voor Keel-Neus-Oorheelkunde en Heelkunde van het Hoofd-Halsgebied.
- Mw. M.C. (Mariëtte) Koster – Klaver, beleidsmedewerker OK, Nederlandse Vereniging van Anesthesiemedewerkers.
- Mw. R. (Rina) Koopman – Kuijl, operatieassistent/wondverpleegkundige, Landelijke Vereniging van Operatieassistenten.

Met ondersteuning van:

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Samenvatting

Module Mechanical Bowel Preparation

Clinical question
What is the effect of different methods of bowel preparation on the incidence of surgical site infections (SSI), anastomotic leakage (AL) and mortality in patients undergoing elective colorectal surgery?

Wat is het effect van verschillende methode van darmvoorbereiding op het aantal chirurgische wondinfecties, naadlekkages en mortaliteit bij patiënten die electieve colorectale chirurgie ondergaan?

Aanbeveling

Behandel (bij voorkeur) patiënten voorafgaand aan colorectale chirurgie, ter preventie van postoperatieve wondinfecties en naadlekkages, met de volgende darmvoorbereiding:

- **Alleen orale antibiotica, of**
- **Orale antibiotica in combinatie met mechanische darmvoorbereiding**

Bespreek met patiënten de voor- en nadelen van mechanische darmvoorbereiding.

Behandel patiënten voorafgaand aan colorectale chirurgie niet met alleen mechanische darmvoorbereiding met als doel preventie van postoperatieve wondinfecties en naadlekkages.

Module Skin Preparation

Clinical question
What is the effect of different preoperative skin antiseptic solutions and concentrations on the risk of surgical site infections in surgical patients?

Wat is het effect van verschillende concentraties van preoperatieve desinfectiemiddelen ter voorkoming van chirurgische wondinfecties bij patiënten die een chirurgische ingreep ondergaan?

Aanbeveling

Gebruik voorafgaand aan chirurgische interventies 2.0-2.5% chloorhexidine-alcohol voor het desinfecteren van de huid van de patiënt, ter preventie van postoperatieve wondinfecties.

- *Voor schone chirurgische interventies kan geen specifieke concentratie chloorhexidine-alcohol worden aanbevolen.*

Verantwoording

Autorisatie en geldigheid

Autorisatiedatum:	volgt
Eerstvolgende beoordeling actualiteit	volgt
Geautoriseerd door:	volgt
Belangrijkste wijzigingen t.o.v. vorige versie:	N.v.t.
Regiehouder(s):	Nederlandse Vereniging voor Heelkunde

Algemene gegevens

De ontwikkeling/herziening van deze richtlijnmodule werd ondersteund door het Kennisinstituut van de Federatie Medisch Specialisten (www.demedischspecialist.nl/kennisinstituut) en werd gefinancierd uit de Kwaliteitsgelden Medisch Specialisten (SKMS). De financier heeft geen enkele invloed gehad op de inhoud van de richtlijnmodule.

Samenstelling werkgroep

Voor het ontwikkelen van de richtlijnmodule is in 2020 een multidisciplinaire werkgroep ingesteld, bestaande uit vertegenwoordigers van alle relevante specialismen (zie hiervoor de Samenstelling van de werkgroep) die betrokken zijn bij de zorg voor preventie van postoperatieve wondinfecties.

Belangenverklaringen

De Code ter voorkoming van oneigenlijke beïnvloeding door belangenverstrengeling is gevolgd. Alle werkgroepleden hebben schriftelijk verklaard of zij in de laatste drie jaar directe financiële belangen (betrekking bij een commercieel bedrijf, persoonlijke financiële belangen, onderzoeksfinanciering) of indirecte belangen (persoonlijke relaties, reputatiemanagement) hebben gehad. Gedurende de ontwikkeling of herziening van een module worden wijzigingen in belangen aan de voorzitter doorgegeven. De belangenverklaring wordt opnieuw bevestigd tijdens de commentaarfase.
Een overzicht van de belangen van werkgroepleden en het oordeel over het omgaan met eventuele belangen vindt u in onderstaande tabel. De ondertekende belangenverklaringen zijn op te vragen bij het secretariaat van het Kennisinstituut van de Federatie Medisch Specialisten.

Werkgroeplid	Functie	Nevenfuncties	Gemelde belangen	Ondernomen actie
Mevr. prof. dr. M.A. Boermeester	Chirurg	* Medisch Ethische Commissie, Amsterdam UMC, locatie AMC * Antibiotica Commissie, Amsterdam UMC	Persoonlijke financiële belangen Hieronder staan de beroepsmatige relaties met bedrijfsleven vermeld waarbij eventuele financiële belangen via de AMC Research B.V. lopen, dus	Geen.

			institutionele en geen persoonlijke gelden zijn: Skillslab instructeur e/of spreker (consultant) voor KCI/3M, Smith&Nephew, Johnson&Johnson, Gore, BD/Bard, TELABio, GDM. <u>Persoonlijke relaties</u> Geen. <u>Extern gefinancierd onderzoek</u> Institutionele grants van KCI/3M, Johnson&Johnson en New Compliance. <u>Intellectuele belangen en reputatie</u> Ik maak me sterk voor een 100% evidence-based benadering van maken van aanbevelingen, volledig transparant en reproduceerbaar. Dat is mijn enige belang in deze, geen persoonlijk gewin. <u>Overige belangen</u> Geen.	
Dhr. dr. M.J. van der Laan	Vaatchirurg	Vice voorzitter Consortium Kwaliteit van Zorg NFU, onbetaald	<u>Persoonlijke financiële belangen</u> Geen.	Geen.

			<u>Persoonlijke relaties</u> Geen. <u>Extern gefinancierd onderzoek</u> Geen. <u>Intellectuele belangen en reputatie</u> Geen. <u>Overige belangen</u> Geen.	
Dhr. dr. F.F.A. Ijpma	Traumachirurg	Geen.	<u>Persoonlijke financiële belangen</u> Geen. <u>Persoonlijke relaties</u> Geen. <u>Extern gefinancierd onderzoek</u> Geen. <u>Intellectuele belangen en reputatie</u> Geen. <u>Overige belangen</u> Geen.	Geen.
Dhr. dr. W.C. van der Zwet	Arts-microbioloog	Lid Regionaal Coördinatie Team, Limburgs infectiepreventie & ABR Zorgnetwerk (onbetaald)	<u>Persoonlijke financiële belangen</u> Geen. <u>Persoonlijke relaties</u> Geen.	

			Extern gefinancierd onderzoek Geen. Intellectuele belangen en reputatie Geen. Overige belangen Geen.	
Dhr. dr. P. Segers	Cardiothoracaal chirurg	Geen.	Persoonlijke financiële belangen Geen. Persoonlijke relaties Geen. Extern gefinancierd onderzoek Geen. Intellectuele belangen en reputatie Geen. Overige belangen Geen.	Geen.
Dhr. dr. D.R. Buis	Neurochirurg	Lid Hoofdredactieraad Tijdschrift voor Neurologie & Neurochirurgie - onbetaald	Persoonlijke financiële belangen Geen. Persoonlijke relaties Geen. Extern gefinancierd onderzoek Geen.	Geen.

			Intellectuele belangen en reputatie Geen. Overige belangen Geen.	
Mw. Y.E.M. Dreissen	AIOS neurochirurgie	Geen.	Persoonlijke financiële belangen Geen. Persoonlijke relaties Geen. Extern gefinancierd onderzoek Geen. Intellectuele belangen en reputatie Geen. Overige belangen Geen.	Geen.
Dhr. R.R. Schaad	Anesthesioloog	Geen.	Persoonlijke financiële belangen Geen. Persoonlijke relaties Geen. Extern gefinancierd onderzoek Geen. Intellectuele belangen en reputatie Geen. Overige belangen Geen.	Geen.

Dhr. dr. J.H.M. Goosen	Orthopaedisch Chirurg	Inhoudelijke presentaties voor Smith&Nephew en Zimmer Biomet. Deze worden vergoed per uur	<u>Persoonlijke financiële belangen</u> Geen. <u>Persoonlijke relaties</u> Geen. <u>Extern gefinancierd onderzoek</u> Geen. <u>Intellectuele belangen en reputatie</u> Geen. <u>Overige belangen</u> Geen.	Geen.

Inbreng patiëntenperspectief

Er werd aandacht besteed aan het patiëntenperspectief door uitnodigen van de Patiëntenfederatie Nederland voor de invitational conference. De verkregen input is meegenomen bij het opstellen van de uitgangsvragen, de keuze voor de uitkomstmaten en bij het opstellen van de overwegingen. De conceptmodules zijn tevens voor commentaar voorgelegd aan de Patiëntenfederatie Nederland en de eventueel aangeleverde commentaren zijn bekeken en verwerkt.

Wkkgz & Kwalitatieve raming van mogelijke substantiële financiële gevolgen

Kwalitatieve raming van mogelijke financiële gevolgen in het kader van de Wkkgz
Bij de richtlijn is conform de Wet kwaliteit, klachten en geschillen zorg (Wkkgz) een kwalitatieve raming uitgevoerd of de aanbevelingen mogelijk leiden tot substantiële financiële gevolgen. Bij het uitvoeren van deze beoordeling zijn richtlijnmodules op verschillende domeinen getoetst (zie het stroomschema op de Richtlijnendatabase).

Uit de kwalitatieve raming blijkt dat er waarschijnlijk geen substantiële financiële gevolgen zijn, zie onderstaande tabel.

Module	**Uitkomst raming**	**Toelichting**
Module 2: Mechanical bowel preparation	geen financiële gevolgen	Uitkomst 3
Module 3: Skin preparation	geen financiële gevolgen	Uitkomst 3

De kwalitatieve raming volgt na de commentaarfase.

Werkwijze

AGREE

Deze richtlijnmodule is opgesteld conform de eisen vermeld in het rapport Medisch Specialistische Richtlijnen 2.0 van de adviescommissie Richtlijnen van de Raad Kwaliteit. Dit rapport is gebaseerd op het AGREE II instrument (Appraisal of Guidelines for Research & Evaluation II; Brouwers, 2010).

Knelpuntenanalyse en uitgangsvragen

Tijdens de voorbereidende fase inventariseerde de werkgroep de knelpunten in de zorg voor patiënten die chirurgie ondergaan. Tevens zijn er knelpunten aangedragen door middel van een invitational conference. Een verslag hiervan is opgenomen onder aanverwante producten.

Op basis van de uitkomsten van de knelpuntenanalyse zijn door de werkgroep concept-uitgangsvragen opgesteld en definitief vastgesteld.

Uitkomstmaten

Na het opstellen van de zoekvraag behorende bij de uitgangsvraag inventariseerde de werkgroep welke uitkomstmaten voor de patiënt relevant zijn, waarbij zowel naar gewenste als ongewenste effecten werd gekeken. Hierbij werd een maximum van acht uitkomstmaten gehanteerd. De werkgroep waardeerde deze uitkomstmaten volgens hun relatieve belang bij de besluitvorming rondom aanbevelingen, als cruciaal (kritiek voor de besluitvorming), belangrijk (maar niet cruciaal) en onbelangrijk. Tevens definieerde de werkgroep tenminste voor de cruciale uitkomstmaten welke verschillen zij klinisch (patiënt) relevant vonden.

Methode literatuursamenvatting

Een uitgebreide beschrijving van de strategie voor zoeken en selecteren van literatuur is te vinden onder 'Zoeken en selecteren' onder Onderbouwing. Indien mogelijk werd de data uit verschillende studies gepoold in een random-effects model. De beoordeling van de kracht van het wetenschappelijke bewijs wordt hieronder toegelicht.

Beoordelen van de kracht van het wetenschappelijke bewijs

De kracht van het wetenschappelijke bewijs werd bepaald volgens de GRADE-methode. GRADE staat voor 'Grading Recommendations Assessment, Development and Evaluation' (zie http://www.gradeworkinggroup.org/). De basisprincipes van de GRADE-methodiek zijn: het benoemen en prioriteren van de klinisch (patiënt) relevante uitkomstmaten, een systematische review per uitkomstmaat, en een beoordeling van de bewijskracht per uitkomstmaat op basis van de acht GRADE-domeinen (domeinen voor downgraden: risk of bias, inconsistentie, indirectheid, imprecisie, en publicatiebias; domeinen voor upgraden: dosis-effect relatie, groot effect, en residuele plausibele confounding).
GRADE onderscheidt vier gradaties voor de kwaliteit van het wetenschappelijk bewijs: hoog, redelijk, laag en zeer laag. Deze gradaties verwijzen naar de mate van zekerheid die er bestaat over de literatuurconclusie, in het bijzonder de mate van zekerheid dat de literatuurconclusie de aanbeveling adequaat ondersteunt (Schünemann, 2013; Hultcrantz, 2017).

GRADE	Definitie
Hoog	– er is hoge zekerheid dat het ware effect van behandeling dichtbij het geschatte effect van behandeling ligt;

	– het is zeer onwaarschijnlijk dat de literatuurconclusie klinisch relevant verandert wanneer er resultaten van nieuw grootschalig onderzoek aan de literatuuranalyse worden toegevoegd.
Redelijk	– er is redelijke zekerheid dat het ware effect van behandeling dichtbij het geschatte effect van behandeling ligt; – het is mogelijk dat de conclusie klinisch relevant verandert wanneer er resultaten van nieuw grootschalig onderzoek aan de literatuuranalyse worden toegevoegd.
Laag	– er is lage zekerheid dat het ware effect van behandeling dichtbij het geschatte effect van behandeling ligt; – er is een reële kans dat de conclusie klinisch relevant verandert wanneer er resultaten van nieuw grootschalig onderzoek aan de literatuuranalyse worden toegevoegd.
Zeer laag	– er is zeer lage zekerheid dat het ware effect van behandeling dichtbij het geschatte effect van behandeling ligt; – de literatuurconclusie is zeer onzeker.

Bij het beoordelen (graderen) van de kracht van het wetenschappelijk bewijs in richtlijnen volgens de GRADE-methodiek spelen grenzen voor klinische besluitvorming een belangrijke rol (Hultcrantz, 2017). Dit zijn de grenzen die bij overschrijding aanleiding zouden geven tot een aanpassing van de aanbeveling. Om de grenzen voor klinische besluitvorming te bepalen moeten alle relevante uitkomstmaten en overwegingen worden meegewogen. De grenzen voor klinische besluitvorming zijn daarmee niet één op één vergelijkbaar met het minimaal klinisch relevant verschil (Minimal Clinically Important Difference, MCID). Met name in situaties waarin een interventie geen belangrijke nadelen heeft en de kosten relatief laag zijn, kan de grens voor klinische besluitvorming met betrekking tot de effectiviteit van de interventie bij een lagere waarde (dichter bij het nuleffect) liggen dan de MCID (Hultcrantz, 2017).

Overwegingen (van bewijs naar aanbeveling)

Om te komen tot een aanbeveling zijn naast (de kwaliteit van) het wetenschappelijke bewijs ook andere aspecten belangrijk en worden meegewogen, zoals aanvullende argumenten uit bijvoorbeeld de biomechanica of fysiologie, waarden en voorkeuren van patiënten, kosten (middelenbeslag), aanvaardbaarheid, haalbaarheid en implementatie. Deze aspecten zijn systematisch vermeld en beoordeeld (gewogen) onder het kopje 'Overwegingen' en kunnen (mede) gebaseerd zijn op expert opinion. Hierbij is gebruik gemaakt van een gestructureerd format gebaseerd op het evidence-to-decision framework van de internationale GRADE Working Group (Alonso-Coello, 2016a; Alonso-Coello 2016b). Dit evidence-to-decision framework is een integraal onderdeel van de GRADE methodiek.

Formuleren van aanbevelingen

De aanbevelingen geven antwoord op de uitgangsvraag en zijn gebaseerd op het beschikbare wetenschappelijke bewijs en de belangrijkste overwegingen, en een weging van de gunstige en ongunstige effecten van de relevante interventies. De kracht van het wetenschappelijk bewijs en het gewicht dat door de werkgroep wordt toegekend aan de overwegingen, bepalen samen de sterkte van de aanbeveling. Conform de GRADE-methodiek sluit een lage bewijskracht van conclusies in de systematische literatuuranalyse een sterke aanbeveling niet a priori uit, en zijn bij een hoge bewijskracht ook zwakke aanbevelingen mogelijk (Agoritsas, 2017; Neumann, 2016). De sterkte van de aanbeveling wordt altijd bepaald door weging van alle relevante argumenten tezamen. De werkgroep

heeft bij elke aanbeveling opgenomen hoe zij tot de richting en sterkte van de aanbeveling zijn gekomen.
In de GRADE-methodiek wordt onderscheid gemaakt tussen sterke en zwakke (of conditionele) aanbevelingen. De sterkte van een aanbeveling verwijst naar de mate van zekerheid dat de voordelen van de interventie opwegen tegen de nadelen (of vice versa), gezien over het hele spectrum van patiënten waarvoor de aanbeveling is bedoeld. De sterkte van een aanbeveling heeft duidelijke implicaties voor patiënten, behandelaars en beleidsmakers (zie onderstaande tabel). Een aanbeveling is geen dictaat, zelfs een sterke aanbeveling gebaseerd op bewijs van hoge kwaliteit (GRADE gradering HOOG) zal niet altijd van toepassing zijn, onder alle mogelijke omstandigheden en voor elke individuele patiënt.

Implicaties van sterke en zwakke aanbevelingen voor verschillende richtlijngebruikers		
	Sterke aanbeveling	*Zwakke (conditionele) aanbeveling*
Voor patiënten	De meeste patiënten zouden de aanbevolen interventie of aanpak kiezen en slechts een klein aantal niet.	Een aanzienlijk deel van de patiënten zouden de aanbevolen interventie of aanpak kiezen, maar veel patiënten ook niet.
Voor behandelaars	De meeste patiënten zouden de aanbevolen interventie of aanpak moeten ontvangen.	Er zijn meerdere geschikte interventies of aanpakken. De patiënt moet worden ondersteund bij de keuze voor de interventie of aanpak die het beste aansluit bij zijn of haar waarden en voorkeuren.
Voor beleidsmakers	De aanbevolen interventie of aanpak kan worden gezien als standaardbeleid.	Beleidsbepaling vereist uitvoerige discussie met betrokkenheid van veel stakeholders. Er is een grotere kans op lokale beleidsverschillen.

Organisatie van zorg

In de knelpuntenanalyse en bij de ontwikkeling van de richtlijnmodule is expliciet aandacht geweest voor de organisatie van zorg: alle aspecten die randvoorwaardelijk zijn voor het verlenen van zorg (zoals coördinatie, communicatie, (financiële) middelen, mankracht en infrastructuur). Randvoorwaarden die relevant zijn voor het beantwoorden van deze specifieke uitgangsvraag zijn genoemd bij de overwegingen. Meer algemene, overkoepelende, of bijkomende aspecten van de organisatie van zorg worden behandeld in de module Organisatie van zorg.

Commentaar- en autorisatiefase

De conceptrichtlijnmodule werd aan de betrokken (wetenschappelijke) verenigingen en (patiënt) organisaties voorgelegd ter commentaar. De commentaren werden verzameld en besproken met de werkgroep. Naar aanleiding van de commentaren werd de conceptrichtlijnmodule aangepast en definitief vastgesteld door de werkgroep. De definitieve richtlijnmodule werd aan de deelnemende (wetenschappelijke) verenigingen en (patiënt) organisaties voorgelegd voor autorisatie en door hen geautoriseerd dan wel geaccordeerd.

Literatuur

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Mechanical bowel preparation

Clinical question

What is the effect of different methods of bowel preparation on the incidence of surgical site infections (SSI), anastomotic leakage (AL) and mortality in patients undergoing elective colorectal surgery?

Introduction

Surgical site infections (SSI) and anastomotic leakage (AL) are serious complications after colorectal surgery and associated with high morbidity, mortality, and costs. Incidence of 5-25% for SSI and 3-12% for AL have been reported. Bowel preparation may prevent a large proportion of SSI and can be performed using mechanical bowel preparation (MBP), oral antibiotics alone (OA) and a combination of both (MBP-OA). Here, we provide an up-to-date evaluation on the effect of different methods of bowel preparation on surgical site infections, anastomotic leakage, and mortality after elective colorectal surgery.

Search and select

A systematic review of the literature was performed to answer the following question:

P: Adults undergoing elective colorectal surgery.
I: Mechanical bowel preparation (MBP), oral antibiotics alone (OA), a combination of oral antibiotics and mechanical bowel preparation (MBP-OA).
C: No bowel preparation, MBP, OA, or MBP-OA.
O: Surgical site infections (SSI), anastomotic leakage, mortality.

Relevant outcome measures

The guideline development group considered the occurrence of surgical site infections as a critical outcome measure for decision making; and anastomotic leakage and mortality as important outcome measures for clinical decision making.

The working group defined a threshold of 10% for continuous outcomes and a relative risk (RR) for dichotomous outcomes of <0.80 and >1.25 as a minimal clinically (patient) important difference.

Search and select (Methods)

The databases Pubmed, Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 10-08-2021. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 3040 hits, eight additional studies were found through forward and backward citation tracking. Studies were selected based on the following criteria: systematic reviews and RCTs on the question of the effect of MBP with oral antibiotics, MBP alone, and oral antibiotics alone. One hundred twenty-three studies were initially selected based on title and abstract screening. After reading the full text, 75 studies were excluded (see the exclusion table with reasons for exclusion), and 48 studies were included.

Results

Forty-eight studies were included in the final analysis. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Summary of literature

Description of studies

Forty-eight RCTs were included in the analysis of the literature, involving 13,611 patients. In total, 23 RCTs compared MBP-OA and MBP (Abis, 2019; Anjum, 2017; Espin-Basany, 2005; Coppa, 1988; Hata, 2016; Horie, 2007; Ikeda, 2016; Ishida, 2001; Kobayashi, 2007; Lau, 1988; Lewis, 2002; Oshima, 2013; Papp, 2021; Playforth, 1988; Reynolds, 1989; Roos, 2011; Rybakov, 2021; Sadahiro, 2013; Schardey, 2020; Stellato, 1990; Takesue, 2000; Taylor, 1994; Uchino, 2019), sixteen RCTs compared MBP and no preparation (Bertani, 2011; Bhat, 2016; Bhattacharjee, 2015; Bretagnol, 2010; Bucher, 2005; Burke, 1994; Contant, 2007; Fa-Si-Oen, 2005; Jung, 2007; Mai-Phan, 2019; Miettinen, 2000; Pena-Soria, 2008; Platell, 2006; Ram, 2005; Sasaki, 2012; Watanabe, 2010), five RCTs compared OA with no preparation (Arezzo, 2021; Espin-Basany, 2020; Hanel, 1980; Mulder, 2020; Viddal, 1980), three RCTs compared OA and MBP-OA (Suzuki, 2020; Zmora, 2003; Zmora, 2006) and one RCT compared MBP-OA and no preparation (Koskenvuo, 2019).

The following solutions were used for MBP, alone or in combination with others: polyethylene glycol solution (n=24), sodium picosulfate (n=10), sodium phosphate (n=8), magnesium citrate (n=5), bisacodyl (n=2), mannitol (n=1), and senna (n=1). Risk of bias was assessed with the Cochrane Risk of Bias-2 (RoB2) tool. The reported outcomes were surgical site infections.

The protocols regarding OA in the 32 studies varied greatly. Aminoglycocides (e.g., kanamycin, neomycin, erythromycin) were used in 27 out of 32 studies, of which in fourteen studies in combination with metronidazole. OA were usually started the day before surgery. Alternative protocols span from three days preoperative until postoperative day seven, ranging from two till four times a day. Cephalosporins (1 to 2 grams) alone or in combination with metronidazole (0.5 to 1 grams), or flomoxef (1 gram) were often used for preoperative surgical antibiotic prophylaxis (SAP). Redosing of SAP during surgery was performed in fifteen out of 48 studies, if surgery lasted longer than two to four hours depending on the half-life of antibiotics used.

1. Surgical site infections (SSI)

A network meta-analysis was carried out to investigate the effect of the different treatment modalities on SSI. In total, 47 RCTs contributed to the overall NMA. A network graph, including all studies is presented in figure 1.

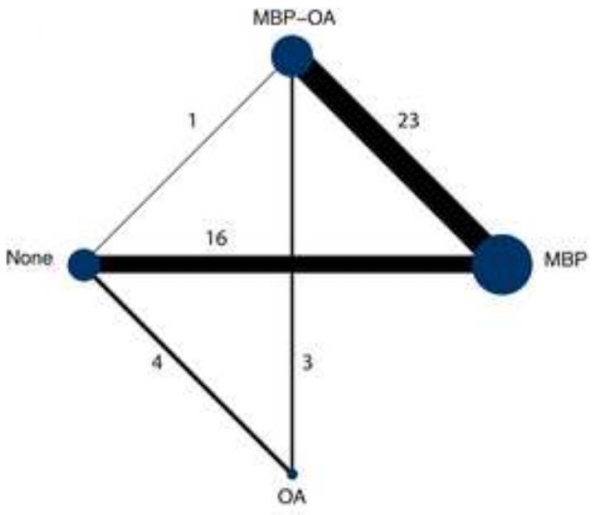

Figure 1. Network graph of all studies for outcome surgical site infections in network meta-analysis (Jalalzadeh, 2022)

1.1 MBP-OA versus OA

In total, three studies (n=880) contributed with a direct comparison to the NMA investigating the effect of MBP-OA versus OA on SSI (Suzuki, 2020; Zmora, 2006; Zmora, 2003). The overall network RR was 0.84 (95% CI 0.60, 1.19), a non-significant nor clinically relevant difference between groups.

1.2 MBP-OA versus MBP

In total, twenty-three studies (n=6197) contributed with a direct comparison to the NMA investigating the effect of MBP-OA versus MBP on SSI (Abis, 2019; Anjum, 2017; Coppa, 1988; Espin-Basany, 2005; Hata, 2016; Horie, 2007; Ikeda, 2016; Ishida, 2001; Kobayashi, 2007; Lau, 1988; Lewis, 2002; Oshima, 2013; Papp, 2021; Playforth, 1988; Reynolds, 1989; Roos, 2011; Rybakov, 2021; Sadahiro, 2013; Schardey, 2020; Stellato, 1990; Takesue, 2000; Taylor, 1994; Uchino, 2019). The overall network RR was 0.55 (95% CI 0.47, 0.65), a significant and clinically relevant difference favoring MBP-OA.

1.3 MBP-OA versus no preparation

In total, one study (n=396) contributed with a direct comparison to the NMA investigating the effect of MBP-OA versus no preparation on SSI (Koskenvuo, 2019). The overall network RR was 0.57 (95% CI 0.45, 0.72), a significant and clinically relevant difference favoring MBP-OA.

1.4 OA versus MBP

There were no studies that contributed with a direct comparison to the NMA investigating the effect of OA versus MBP on SSI. Therefore, indirect estimates of the comparison of OA versus MBP in the NMA were reported. The overall network RR was 0.65 (95% CI 0.46,0.92), a significant and clinically relevant difference favoring OA.

1.5 OA versus no preparation

In total, five studies (n=927) contributed with a direct comparison to the NMA investigating the effect of OA versus no preparation on SSI (Mulder, 2020; Arezzo, 2021; Espin-Basany, 2020; Hanel, 1980; Viddal, 1980). The overall network RR was 0.68 (95% CI 0.49, 0.95), a significant and clinically relevant difference favoring OA.

1.6 MPB versus no preparation

In total, sixteen studies (n=5211) contributed with a direct comparison to the NMA investigating the effect of MPB versus no preparation on SSI (Bertani, 2011; Bhat, 2016; Bhattacharjee, 2015; Bretagnol, 2010; Bucher, 2005; Burke, 1994; Contant, 2007; Fa-Si-Oen, 2005; Jung, 2007; Mai-Phan, 2019; Miettinen, 2000; Pena-Soria, 2008; Platell, 2006; Ram, 2005; Sasaki, 2012; Watanabe, 2010). The overall network RR was 1.05 (95% CI 0.87, 1.26), a non-significant nor clinically relevant difference between groups.

2. Anastomotic leakage

A network meta-analysis was carried out to investigate the effect of the different treatment modalities on anastomotic leakage. In total, 39 RCTs contributed to the overall NMA. A network graph, including all studies is presented in figure 2.

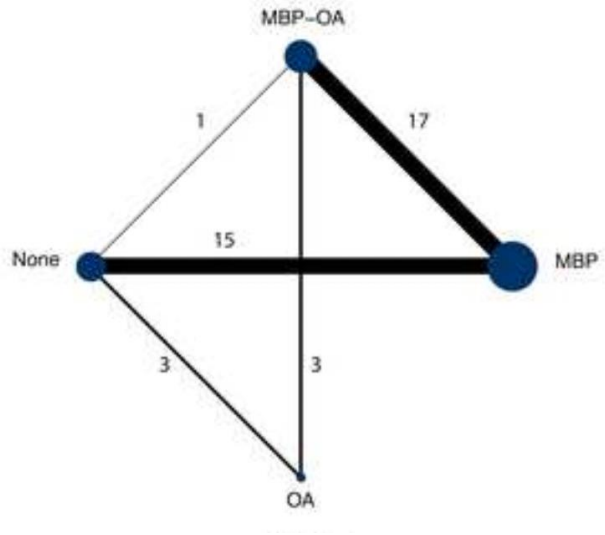

Figure 2. Network graph of all studies for outcome anastomotic leakage in network meta-analysis (Jalalzadeh, 2022)

2.1 MBP-OA versus OA

In total, three studies (n=880) contributed with a direct comparison to the NMA investigating the effect of MBP-OA versus OA on AL (Suzuki, 2020; Zmora, 2003; Zmora, 2006). The overall network RR was 0.76 (95% CI 0.51, 1.15), a non-significant but clinically relevant difference favoring MBP-OA.

2.2 MBP-OA versus MBP

In total, eighteen studies (n=4173) contributed with a direct comparison to the NMA investigating the effect of MBP-OA versus MBP on AL (Abis, 2019; Anjum, 2017; Coppa, Espin-Basany, 2005; 1988; Hata, 2016; Horie, 2007; Ikeda, 2016; Ishida, 2001; Lau, 1988; Papp, 2021; Playforth, 1988; Roos, 2011; Rybakov, 2020; Sadahiro, 2014; Schardey, 2020; Stellato, 1990; Takesue, 2000; Taylor, 1994;). Espin-Basany (2005) reported zero AL in both arms and was thus excluded from the NMA, leaving 17 studies in the final NMA (figure 2).

Node splitting the results showed this comparison had significant inconsistencies between direct and indirect evidence. The direct evidence has higher quality of evidence, thus we valued the direct comparison over the indirect comparison (and use this for our conclusion).

The overall direct RR was 0.55 (95% CI 0.40, 0.76), a significant and clinically relevant difference favoring MBP-OA.

2.3 MBP-OA versus no preparation

In total, one study (n=396) contributed with a direct comparison to the NMA investigating the effect of MBP-OA versus no preparation on AL (Koskenvuo, 2019). The overall network RR was 0.59 (95% CI 0.42, 0.84), a significant and clinically relevant difference favoring MBP-OA.

2.4 OA versus MBP

There were no studies that contributed with a direct comparison to the NMA investigating the effect of OA versus MBP on AL. Therefore, only the indirect estimates of the comparison between OA and MBP was reported. The overall network RR was 0.83 (95% CI 0.59, 1.17), a non-significant nor clinically relevant difference between groups.

2.5 OA versus no preparation

In total, four studies (n=860) contributed with a direct comparison to the NMA investigating the effect of OA versus no preparation on AL (Arezzo, 2021; Espin-Basany, 2020; Mulder,

2020; Vidal, 1980). Vidal (1980) reported zero AL in both arms and was thus excluded from the NMA, leaving three studies in the final NMA (figure 2). The overall network RR was 0.78 (95% CI 0.61, 0.99), a significant and clinically relevant difference favoring OA.

2.6 MPB versus no preparation

In total, sixteen studies (n=5211) contributed with a direct comparison to the NMA investigating the effect of MBP versus no preparation on AL (Bertani, 2011; Bhat, 2016; Bhattacharjee, 2015; Bretagnol, 2010; Bucher, 2005; Burke, 1994; Contant, 2007; Fa-Si-Oen, 2005; Jung, 2007; Mai-Phan, 2019; Miettinen, 2000; Pena-Soria, 2008; Platell, 2006; Ram, 2005; Sasaki, 2012; Watanabe, 2010). Watanabe (2010) reported zero AL in both arms and was thus excluded from the NMA, leaving 15 studies in the final NMA (figure 2).
Node splitting the results showed this comparison had significant inconsistencies between direct and indirect evidence. The direct evidence has higher quality of evidence, thus we valued the direct comparison over the indirect comparison (and use this for our conclusion). The overall direct RR was 0.85 (95% CI 0.65, 1.11), a non-significant nor clinically relevant difference.

3. Mortality

A network meta-analysis was carried out to investigate the effect of the different treatment modalities on mortality. In total, 20 RCTs contributed to the overall NMA. A network graph, including all studies is presented in figure 3.

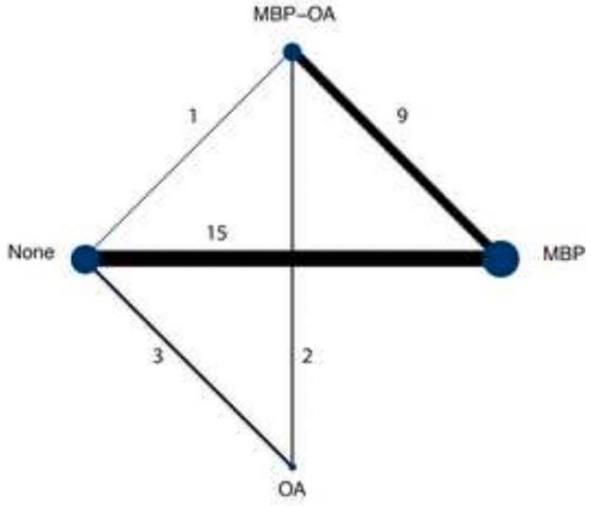

Figure 3. Network graph of all studies for outcome mortality in network meta-analysis (Jalalzadeh, 2022)

3.1 MBP-OA versus OA

In total, three studies (n=880) contributed with a direct comparison to the NMA investigating the effect of MBP-OA versus OA on mortality (Suzuki, 2020; Zmora, 2013; Zmora, 2016). Suzuki (2020) reported zero deaths in both arms and was thus excluded from the NMA, leaving 2 studies in the final NMA (figure 3). The overall network RR was 0.82 (95% CI 0.26, 2.57), a non-significant nor clinically relevant difference between groups.

3.2 MBP-OA versus MBP

In total, eleven studies (n=3062) contributed with a direct comparison to the NMA investigating the effect of MBP-OA versus MBP on mortality (Abis, 2019; Coppa, 1988; Horie, 2007; Ikeda, 2016; Lewis, 2002; Papp, 2021; Playforth, 1988; Roos, 2011; Schardey, 2020;

Stellato, 1990; Taylor, 1994). Ikeda (2016) and Horie (2007) reported zero deaths in both arms and were excluded from the NMA, leaving 9 studies in the final NMA (figure 3). The overall network RR was 1.05 (95% CI 0.63, 1.75), a non-significant nor clinically relevant difference between groups.

3.3 MBP-OA versus no preparation

In total, one study (n=396) contributed with a direct comparison to the NMA investigating the effect of MBP-OA versus no preparation on mortality (Koskenvuo, 2019). The overall network RR was 0.99 (95% CI 0.51, 1.91), a non-significant nor clinically relevant difference between groups.

3.4 OA versus MBP

There were no studies that contributed with a direct comparison to the NMA investigating the effect of OA versus MBP on mortality. Therefore, indirect estimates of the comparison of OA versus MBP in the NMA were reported. The overall network RR was 1.28 (95% CI 0.39, 4.25), a non-significant nor clinically relevant difference between groups.

3.5 OA versus no preparation

In total, two studies (n=282) contributed with a direct comparison to the NMA investigating the effect of OA versus no preparation on mortality (Arezzo, 2021; Mulder, 2020). Mulder (2020) reported zero deaths in both arms and was thus excluded from the NMA, leaving one study in the final NMA (figure 3). The overall network RR was 1.21 (95% CI 0.35, 4.12), a non-significant nor clinically relevant difference between groups.

3.6 MPB versus no preparation

In total, fourteen studies (n=5090) contributed with a direct comparison to the NMA investigating the effect of MBP versus no preparation on mortality (Bhat, 2016; Bertani, 2011; Bhattacharjee, 2015; Bretagnol, 2010; Bucher, 2005; Burke, 1994; Contant, 2007; Fa-Si-Oen, 2005; Jung, 2007; Mai-Phan, 2019; Miettinen, 2000; Pena-Soria, 2008; Platell, 2006; Ram, 2005). The overall RR was 0.94 (95% CI 0.60, 1.46), a non-significant nor clinically relevant difference between groups.

Level of evidence of the literature

The GRADE approach for rating the certainty of estimates of treatment effects was used. Since all included studies are randomized controlled trials, the rating for the GRADE starts high for all comparisons. Each comparison can be downgraded due to one of the following reasons: **risk of bias:** the quality assessment of the individual studies is presented in the risk of bias tables; **inconsistency:** similarity of point estimates, extent of overlap of confidence intervals, and statistical criteria including tests of heterogeneity and I^2; **imprecision:** For point estimates with 95%CIs that crosses the null-effect threshold and boundaries for clinical decision making we downgraded with one or two dimensions. If the boundaries are not crossed, we did not downgrade. **Publication bias:** The comparison-adjusted funnel plot showed no sign of small-study effects (see funnel plot diagrams).

If only direct or indirect evidence is available for a given comparison, the network quality rating will be based on that estimate. When, for a particular comparison, both direct and indirect evidence are available, we used the highest of the two quality ratings as the quality rating for the NMA estimate. The quality of the network estimate can be upgraded if precision is greater than direct or indirect estimates.

Table 2. Level of evidence per comparison for surgical site infection, anastomotic leakage, and mortality.

	Reasons for downgrading		
	Direct evidence	**Indirect evidence**	**Network meta-analysis**
Surgical site infections			
MBP-OA vs. OA	-2 imprecision -1 risk of bias	-2 imprecision -1 risk of bias	-2 imprecision -1 risk of bias
MBP-OA vs. MBP	-1 risk of bias	-1 imprecision -1 risk of bias	-1 risk of bias
MBP-OA vs. None	-2 imprecision -1 risk of bias	-1 risk of bias	-1 risk of bias
OA vs. MBP	N.a.	-1 imprecision -1 risk of bias	-1 imprecision -1 risk of bias
OA vs. None	-1 imprecision -1 risk of bias	-1 imprecision -1 risk of bias	-1 imprecision -1 risk of bias
MBP vs. None	-1 imprecision -1 risk of bias	-2 imprecision -1 risk of bias	-1 imprecision -1 risk of bias
Anastomotic leakage			
MBP-OA vs. OA	-2 imprecision -1 risk of bias	-1 imprecision -1 risk of bias	-1 imprecision -1 risk of bias
MBP-OA vs. MBP	-1 risk of bias	-2 imprecision -1 risk of bias	-1 risk of bias
MBP-OA vs. None	-2 imprecision -1 risk of bias	-1 imprecision -1 risk of bias	-1 imprecision -1 risk of bias
OA vs. MBP	N.a	-1 imprecision -1 risk of bias	-1 imprecision -1 risk of bias
OA vs. None	-1 imprecision -1 risk of bias	-1 imprecision -1 risk of bias	-1 imprecision -1 risk of bias
MBP vs. None	-1 imprecision -1 risk of bias	-1 imprecision -1 risk of bias	-1 imprecision -1 risk of bias
Mortality			
MBP-OA vs. OA	-2 imprecision -1 risk of bias	-2 imprecision -1 risk of bias	-2 imprecision -1 risk of bias
MBP-OA vs. MBP	-2 imprecision -1 risk of bias	-2 imprecision -1 risk of bias	-2 imprecision -1 risk of bias
MBP-OA vs. None	N.a.	-2 imprecision -1 risk of bias	-2 imprecision -1 risk of bias
OA vs. MBP	-2 imprecision -1 risk of bias	-2 imprecision -1 risk of bias	-2 imprecision -1 risk of bias
OA vs. None	-2 imprecision -1 risk of bias	-2 imprecision -1 risk of bias	-2 imprecision -1 risk of bias
MBP vs. None	-2 imprecision -1 risk of bias	-2 imprecision -1 risk of bias	-2 imprecision -1 risk of bias

Table 2. Relative risk plus the level of evidence per comparison for surgical site infection, anastomotic leakage, and mortality.

Comparison	Direct evidence		Indirect evidence		Network meta-analysis	
	Relative Risk (95%CI)	Quality of evidence	Relative Risk (95%CI)	Quality of evidence	Relative Risk (95%CI)	Quality of evidence
Surgical Site Infections						
MBP-OA *v* OA	0.85 (0.51 - 1.41)	⊕◯◯◯ Very Low	0.84 (0.52 - 1.35)	⊕⊕◯◯ Low	0.84 (0.60 - 1.19)	⊕⊕◯◯ Low
MBP-OA *v* MBP	**0.55 (0.46 - 0.65)**	⊕⊕⊕◯ Moderate	**0.57 (0.33 - 0.99)**	⊕⊕◯◯ Low	**0.55 (0.47 - 0.65)**	⊕⊕⊕◯ Moderate
MBP-OA *v* None	0.63 (0.28 - 1.42)	⊕◯◯◯ Very Low	**0.57 (0.45 - 0.73)**	⊕⊕⊕◯ Moderate	**0.57 (0.45 - 0.72)**	⊕⊕⊕◯ Moderate
OA *v* MBP	-	-	**0.65 (0.46 – 0.92)**	⊕⊕◯◯ Low	**0.65 (0.46 – 0.92)**	⊕⊕◯◯ Low
OA *v* None	0.68 (0.46 – 1.02)	⊕⊕◯◯ Low	0.68 (0.38 – 1.20)	⊕⊕◯◯ Low	**0.68 (0.49 – 0.95)**	⊕⊕◯◯ Low
MBP *v* None	1.04 (0.85 - 1.27)	⊕⊕◯◯ Low	1.09 (0.64 - 1.87)	⊕⊕◯◯ Low	1.05 (0.87 - 1.26)	⊕⊕◯◯ Low
Anastomotic leakage						
MBP-OA *v* OA	1.66 (0.67 - 4.11)	⊕◯◯◯ Very Low	**0.63 (0.39 - 0.99)**	⊕⊕◯◯ Low	0.76 (0.51 - 1.15)	⊕⊕◯◯ Low
MBP-OA *v* MBP *	**0.55 (0.40 – 0.76)**	⊕⊕⊕◯ Moderate	1.32 (0.63 - 2.78)	⊕◯◯◯ Very Low	**0.63 (0.47 - 0.84)**	⊕⊕⊕◯ Moderate
MBP-OA *v* None	0.89 (0.33 - 2.42)	⊕◯◯◯ Very Low	**0.56 (0.38 - 0.81)**	⊕⊕◯◯ Low	**0.59 (0.42 - 0.84)**	⊕⊕◯◯ Low
OA *v* MBP	-	-	0.83 (0.59 – 1.17)	⊕⊕◯◯ Low	0.83 (0.59 – 1.17)	⊕⊕◯◯ Low
OA *v* None	0.83 (0.64 – 1.07)	⊕⊕◯◯ Low	**0.31 (0.12 – 0.84)**	⊕⊕◯◯ Low	**0.78 (0.61 – 0.99)**	⊕⊕◯◯ Low
MBP *v* None *	0.85 (0.65 - 1.11)	⊕⊕◯◯ Low	2.02 (0.95 - 4.30)	⊕⊕◯◯ Low	0.94 (0.73 - 1.21)	⊕⊕◯◯ Low
Mortality						
MBP-OA *v* OA	1.29 (0.34 - 4.85)	⊕◯◯◯ Very Low	0.21 (0.02 - 2.05)	⊕◯◯◯ Very Low	0.82 (0.26 - 2.57)	⊕◯◯◯ Very Low
MBP-OA *v* MBP	1.00 (0.59 - 1.69)	⊕◯◯◯ Very Low	0.32 (0.03 -3.57)	⊕◯◯◯ Very Low	0.95 (0.57 - 1.59)	⊕◯◯◯ Very Low
MBP-OA *v* None	0.05 (0.00 - 27.56)	⊕◯◯◯ Very Low	1.02 (0.52 - 1.98)	⊕◯◯◯ Very Low	0.99 (0.51 - 1.91)	⊕◯◯◯ Very Low
OA *v* MBP	-	-	1.28 (0.39 – 4.25)	⊕◯◯◯ Very Low	1.28 (0.39 – 4.25)	⊕◯◯◯ Very Low
OA *v* None	4.16 (0.47 – 36.58)	⊕◯◯◯ Very Low	0.67 (0.15 – 2.99)	⊕◯◯◯ Very Low	1.21 (0.35 – 4.12)	⊕◯◯◯ Very Low
MBP *v* None	0.90 (0.58 - 1.42)	⊕◯◯◯ Very Low	2.81 (0.28 - 31.53)	⊕◯◯◯ Very Low	0.94 (0.60 - 1.46)	⊕◯◯◯ Very Low

** Direct and indirect evidence show significant inconsistency. Thus the focus will be on only the direct evidence, which has a greater confidence than the indirect evidence*

5

Conclusions

Surgical site infections (SSI)

MBP-OA versus OA

Low GRADE	The evidence suggests that mechanical bowel preparation combined with oral antibiotics results in little to no difference in surgical site infections compared to only oral antibiotics in patients undergoing elective colorectal surgery.

MBP-OA versus MBP

Moderate GRADE	Mechanical bowel preparation combined with oral antibiotics likely reduces surgical site infections compared to only mechanical bowel preparation in patients undergoing elective colorectal surgery.

MBP-OA versus None

Moderate GRADE	Mechanical bowel preparation combined with oral antibiotics likely reduces surgical site infections compared with no preparation in patients undergoing elective colorectal surgery.

OA versus MBP

Low GRADE	The evidence suggests only oral antibiotics reduces surgical site infections compared to only mechanical bowel preparation in patients undergoing elective colorectal surgery.

OA versus None

Low GRADE	The evidence suggests only oral antibiotics reduces surgical site infections compared to no preparation in patients undergoing elective colorectal surgery.

MBP versus None

Low GRADE	The evidence suggests that only mechanical bowel preparation results in little to no difference in surgical site infections compared to no preparation in patients undergoing elective colorectal surgery.

Anastomotic leakage

MBP-OA versus OA

Low GRADE	The evidence suggests that mechanical bowel preparation combined with oral antibiotics results in little to no difference of anastomotic leakage compared to only oral antibiotics in patients undergoing elective colorectal surgery.

MBP-OA versus MBP

Moderate GRADE	Mechanical bowel preparation combined with oral antibiotics likely reduces anastomotic leakage compared to only mechanical bowel preparation in patients undergoing elective colorectal surgery.

MBP-OA versus None

Low GRADE	The evidence suggests mechanical bowel preparation combined with oral antibiotics reduces anastomotic leakage compared to no preparation in patients undergoing elective colorectal surgery.

OA versus MBP

Low GRADE	The evidence suggests that only oral antibiotics results in little to no difference of anastomotic leakage compared to only mechanical bowel preparation in patients undergoing elective colorectal surgery.

OA versus None

Low GRADE	The evidence suggests that only oral antibiotics may result in a slight reduction of anastomotic leakage compared with no preparation in patients undergoing elective colorectal surgery.

MBP versus None

Low GRADE	The evidence suggests that mechanical bowel preparation results in little to no difference in anastomotic leakage compared to no preparation in patients undergoing elective colorectal surgery.

Mortality

MBP-OA versus OA

Very low GRADE	The evidence is very uncertain about the effect of mechanical bowel preparation combined with oral antibiotics on mortality compared with only oral antibiotics in patients undergoing elective colorectal surgery.

MBP-OA versus MBP

Very low GRADE	The evidence is very uncertain about the effect of mechanical bowel preparation combined with oral antibiotics on mortality compared to only mechanical bowel preparation in patients undergoing elective colorectal surgery.

MBP-OA versus None

Very Low GRADE	The evidence is very uncertain about the effect of mechanical bowel preparation combined with oral antibiotics on mortality compared to no bowel preparation in patients undergoing elective colorectal surgery.

OA versus MBP

Very low GRADE	The evidence is very uncertain about the effect of only oral antibiotics on mortality compared to mechanical bowel preparation in patients undergoing elective colorectal surgery.

OA versus None

Very low GRADE	The evidence is very uncertain about the effect of only oral antibiotics on mortality compared to no preparation in patients undergoing elective colorectal surgery.

MBP versus None

Very Low GRADE	The evidence is very uncertain about the effect of mechanical bowel preparation on mortality compared to no preparation among patients undergoing elective colorectal surgery.

Considerations – Evidence to decision

Summary of the evidence

The network meta-analysis by Jalalzadeh *et al.* (2022) showed the effect of different types of bowel preparation on the rates of surgical site infections, anastomotic leakage, and mortality for patients undergoing elective colorectal surgery. The results showed a significant reduction of SSI when using MBP-OA or OA alone compared with MBP only or no preparation. MBP-OA and OA showed comparable effectiveness. There was no difference in effect between MBP and no preparation.

Overall, the certainty of evidence was graded as low because of imprecision of the results and risk of bias. Furthermore, MBP-OA and OA may both be effective for the prevention of anastomotic leakage, whereas MBP was not. There was no clear association between the method of bowel preparation and all-cause mortality rate. Only in a sensitivity analysis of studies that focussed on laparoscopic surgery or a mixed laparoscopic/open population, MBP-OA seemed more effective than other methods of bowel preparation including OA alone.

International guidelines

The findings are of added value to existing guideline recommendations. The results are partly in line with current international guidelines but give an important new perspective. WHO (2018) and NICE (2019) guidelines both advise against the use of only MBP as routine preparation. The WHO advises MBP-OA in colorectal surgery. However, both guidelines did not include studies investigating the effect of OA alone. The NICE guidelines acknowledge this limitation and state that their current guideline should be updated with newly published evidence, including studies investigating the effect of OA alone. The current guideline on of the CDC (O'Hara 2018) does not mention bowel preparation. Previous, non-network meta-analyses have shown results in favor of MBP-OA compared to MBP (Rollins 2019) and no clear difference between MBP and no preparation (Güenaga 2011). These results are still in line with present study but lack the relative effect of OA alone. One of the trials investigating the effect of OA alone (Mulder 2020), ended prematurely due to results of a new non-randomized study favoring OA (Mulder 2019). The authors no longer considered clinical equipoise.

The most recent NMA (Woodfield 2022) concludes that OA without MBP shows the greatest reduction in SSI. This is not in line with our findings. Current evidence from present NMA shows that effectiveness of OA alone does not significantly differ from that of MBP-OA (RR 0.84, 95% CI 0.60 – 1.19). Our results support the use of OA alone, but we do not find OA to be superior to MBP-OA. The most recent NMA has not included some of these new RCTs, which explains the difference in results. Some studies were published after the search date, others were excluded for unknown reasons. An earlier NMA (Toh 2018) has identified a knowledge gap with respect to effectiveness of OA as few studies compared OA alone to MBP-OA or no preparation. We included four additional RCTs investigating OA as sole intervention without MBP; all published since 2020. One RCT compared OA alone to MBP-OA (Suzuki 2020) and three studies compared OA alone to no preparation (Arezzo 2021, Espin-Basany 2020, Mulder 2020).

Subgroup: minimal invasive procedures

In recent years, minimally invasive procedures are widely performed and a distinction between effects of the various bowel preparations in open and laparoscopic procedures could be very helpful in clinical practice. Therefore, an additional sensitivity analysis was performed, excluding RCTs with only open surgical procedures. In the remaining cohort for analysis, still 40% of the procedures were open procedures. It was not possible to attribute SSI to either laparoscopic or open surgery among these mixed studies as such details were not supplied in the original publications. Therefore, it is not possible to draw firm recommendations on the

various bowel preparation methods between open and laparoscopic procedures. More studies including only laparoscopic procedures are needed to draw definite conclusions.

Patient preferences

Analysis of effectivity does not take the discomfort and possible harms (e.g., electrolytes imbalance and dehydration) of MBP into consideration nor its practical concerns such as early hospital admission and discomfort for the patient. The harms and benefits should be carefully weighed with patients, ideally using the principles of shared decision making justifying the additional value of MBP to OA.

Resource use

There are no cost-effective studies available.

Sustainability, feasibility, and implementation

There seems to be no issues regarding the feasibility for implementation in clinical practice. Mechanical bowel preparation is often done since no feces can enter the abdominal cavity. Mechanical preparation prior to surgery also gives a better view that may be beneficial during surgery. This may be a barrier for applying OA alone.

Recommendations

Rationale of the recommendation

Present findings revealed that MBP-OA and OA alone reduce SSI compared to no bowel preparation and that MBP-OA results in little to no difference in SSI and AL rates compared to OA alone. Considering additional MBP to OA, one should consider patient preferences, using principles of shared decision making, explaining possible discomfort or harms (e.g., electrolytes imbalance and dehydration) and practical issues.

Behandel (bij voorkeur) patiënten voorafgaand aan colorectale chirurgie, ter preventie van postoperatieve wondinfecties en naadlekkages, met de volgende darmvoorbereiding:

- **Alleen orale antibiotica, of**
- **Orale antibiotica in combinatie met mechanische darmvoorbereiding**

Bespreek met patiënten de voor- en nadelen van mechanische darmvoorbereiding.

Behandel patiënten voorafgaand aan colorectale chirurgie niet met alleen mechanische darmvoorbereiding met als doel preventie van postoperatieve wondinfecties en naadlekkages.

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Skin preparation

Clinical question

What is the effect of different preoperative skin antiseptic solutions and concentrations on the risk of surgical site infections in surgical patients?

Introduction

Surgical site infections (SSI) are the most common postoperative complications and substantially increase morbidity, mortality, and healthcare costs. The efficacy of preoperative skin antiseptics in the prevention of SSIs is well established, but there remains uncertainty about which antiseptic solution and concentration is most effective and international guidelines show discrepancy.

Search and select

A systematic review of the literature was performed to answer the following question:

P: Adults undergoing any surgical procedure
I: Antiseptic skin preparation agents (CHG, iodine or olanexidine) or concentrations in aqueous and alcohol-based solutions.
C: Other antiseptic skin preparation agents (CHG, iodine or olanexidine) or concentrations in aqueous and alcohol-based solutions.
O: Surgical site infections (SSI) (superficial, deep, and organ SSI); adverse events of the intervention (e.g., allergic reactions).

Relevant outcome measures

The guideline development group considered occurrence of surgical site infections as a critical outcome measure for decision making; and adverse events (e.g., allergic reactions) as an important outcome measure for clinical decision making.

The working group defined a threshold of 10% for continuous outcomes and a relative risk (RR) for dichotomous outcomes of <0.80 and >1.25 as a minimal clinically (patient) important difference.

Search and select (Methods)

The databases [Medline (via OVID) and Embase (via Embase.com)] were searched with relevant search terms until 23-11-2021. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 2631 hits.

RCTs were included when comparing two or more antiseptic skin preparation agents (CHG, iodine or olanexidine) or concentrations in aqueous and alcohol-based solutions in adults undergoing surgical procedures in the operating theatre that reported SSI rates.

Sixty-eight studies were initially selected based on title and abstract screening. After reading the full text, 35 studies were excluded (see the exclusion table with reasons for exclusion), and 33 studies were included.

Results

Thirty-three studies were included in the final analysis. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Summary of literature

Description of studies

Thirty-three studies were included in the analysis of the literature, of which 27 RCTs with 17,735 patients were included in the network meta-analysis (NMA). In total, 37 comparisons of treatments were included in the systematic review.

One RCT compared 0.5% CHG-alcohol and 2.0-2.5% CHG-alcohol (Casey, 2015). Three studies compared 0.5% CHG-alcohol with aqueous iodine (Srinivas, 2015; Abreu, 2014; Brown, 1984). Four RCTs compared 0.5% CHG-alcohol and iodine alcohol (Shadid, 2019; Perek, 2013; Cheng, 2009; Veiga, 2008). Eleven studies compared 2.0-2.5% CHG-alcohol and aqueous iodine (NIHR, 2021; Luwang, 2021; Danasekaran, 2017; Springel, 2017; Xu, 2017; Bibi, 2015; Kunkle, 2015; Yeung, 2013; Darouiche, 2010; Sistla, 2010; Saltzman, 2009). Seven RCTs compared 2.0-2.5% CHG-alcohol and iodine alcohol (Ritter, 2020; Broach, 2017; Xu, 2017; Tuuli, 2016; Ngai, 2015; Savage, 2012; Saltzman, 2009). Three RCTs compared 4.0% CHG-alcohol and aqueous iodine (Gezer, 2020; Paocharoen, 2009; Bibbo, 2005). One RCT compared aqueous CHG and aqueous iodine (Park, 2017). Six RCTs compared aqueous iodine and iodine-alcohol (Dior, 2020; Xu, 2017; Saltzman, 2009; Segal, 2002; Howard, 1991; Gilliam, 1990) and one RCT compared aqueous iodine and olanexidine 1.5% (Obara, 2020).

Twenty-seven different solutions were used as skin antiseptics. For the analysis, RCTs using 2.0% and 2.5% CHG in 70% isopropyl alcohol (IPA), alcohol or ethanol were grouped as 2.0-2.5% CHG-alcohol. CHG 0.5% in 70% IPA, alcohol or ethanol were pooled into 0.5% CHG-alcohol. The group 4.0% CHG-alcohol consisted of studies using 4.0% CHG in 70% IPA or alcohol. All formulations of aqueous iodine, aqueous povidone iodine or aqueous iodophor were combined into one group, also for iodine-alcohol, povidone iodine-alcohol and iodophor in alcohol.

1. Surgical site infections (SSI)

A network meta-analysis was carried out to investigate the effect of the different treatment modalities on SSI. In total, 27 RCTs contributed to the overall NMA. A network graph, including all studies is presented in figure 1. Results from the NMA are presented in the forest plots (figure 2).

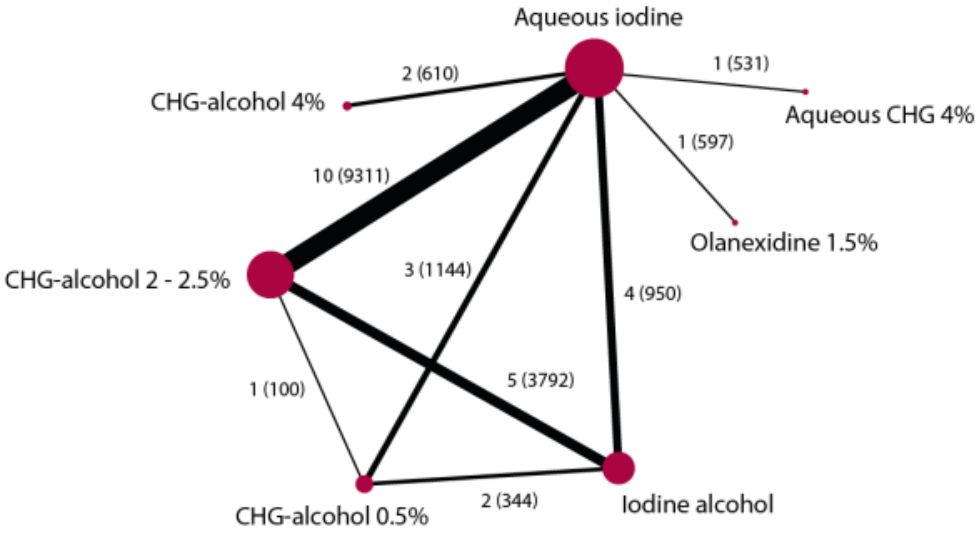


Figure 1. Network graph of all studies in network meta-analysis (Jalalzadeh, 2022; accepted)

1.1 Aqueous iodine versus 0.5% CHG-alcohol

In total, three studies (n=1144) contributed with a direct comparison to the NMA investigating the effect of aqueous iodine versus 0.5% CHG-alcohol on SSI (Srinivas, 2015; Abreu, 2014; Brown, 1984). The overall network RR was 0.69 (95% CI 0.47, 1.02), a non-significant but clinically relevant difference favoring 0.5% CHG-alcohol.

***1.2 Aqueous iodine versus 2.0-2.5% CHG*-alcohol**

In total, ten studies (n=9311) contributed with a direct comparison to the NMA investigating the effect of aqueous iodine versus 4.0% CHG-alcohol on SSI (NIHR 2021, 2021; Luwang, 2021; Danasekaran, 2017; Springel, 2017; Xu, 2017; Bibi, 2015; Kunkle, 2015; Yeung, 2013; Darouiche, 2010; Sistla, 2010). One study (Saltzman, 2009) reported no SSI in both arms and was thus excluded from the NMA. The overall network RR was 0.75 (95% CI 0.61, 0.92), a significant and clinically relevant difference favoring 2.0-2.5% CHG-alcohol.

1.3 Aqueous iodine versus 4.0% CHG-alcohol

In total, two studies (n=610) contributed with a direct comparison to the NMA investigating the effect of aqueous iodine versus 0.5% CHG-alcohol on SSI (Gezer, 2020; Paocharoen, 2009). One study (Bibbo, 2005) reported no SSI in both arms and was thus excluded from the NMA. The overall network RR was 0.67 (95% CI 0.32, 1.40), a non-significant but clinically relevant difference favoring 4.0% CHG-alcohol.

1.4 Aqueous iodine versus aqueous CHG

One study (n=581) contributed with a direct comparison to the NMA investigating the effect of aqueous iodine versus aqueous CHG on SSI (Park, 2017). The overall network RR was 0.93 (95% CI 0.43, 2.01), this difference was not significant nor clinically relevant.

1.5 Aqueous iodine versus iodine-alcohol

In total, four studies (n=950) contributed with a direct comparison to the NMA investigating the effect of aqueous iodine versus iodine-alcohol on SSI (Dior, 2020; Xu, 2017; Segal, 2002; Howard, 1991). Two studies (Saltzman, 2009; Gilliam, 1990) reported no SSI in both arms and were thus excluded from the NMA. The overall network RR was 0.97 (95% CI 0.73, 1.29), this difference was not significant nor clinically relevant.

1.6 Aqueous iodine versus olanexidine 1.5%

One study (n=597) contributed with a direct comparison to the NMA investigating the effect of aqueous iodine versus olanexidine 1.5% on SSI (Obara, 2020). The overall network RR was 0.49 (95% CI 0.26, 0.92), a significant and clinically relevant difference favoring olanexidine 1.5%.

1.7 CHG-alcohol 0.5% versus CHG-alcohol 2.0-2.5%

One study (n=100) contributed with a direct comparison to the NMA investigating the effect of CHG-alcohol 0.5% versus CHG-alcohol 2.0-2.5% on SSI (Casey, 2015). The overall network RR was 0.93 (95% CI 0.60, 1,43), a non-significant nor clinically relevant difference.

1.8 CHG-alcohol 0.5% versus Iodine-alcohol

In total, two studies (n=344) contributed with a direct comparison to the NMA investigating the effect of CHG-alcohol 0.5% versus iodine-alcohol on SSI (Perek, 2013; Veiga, 2008). Two studies (Shadid, 2019; Cheng, 2009) reported no SSI in both arms and were thus excluded from the NMA. The overall network RR was 0.71 (95% CI 0.45, 1.14), a non-significant but clinically relevant difference favoring CHG-alcohol 0.5%.

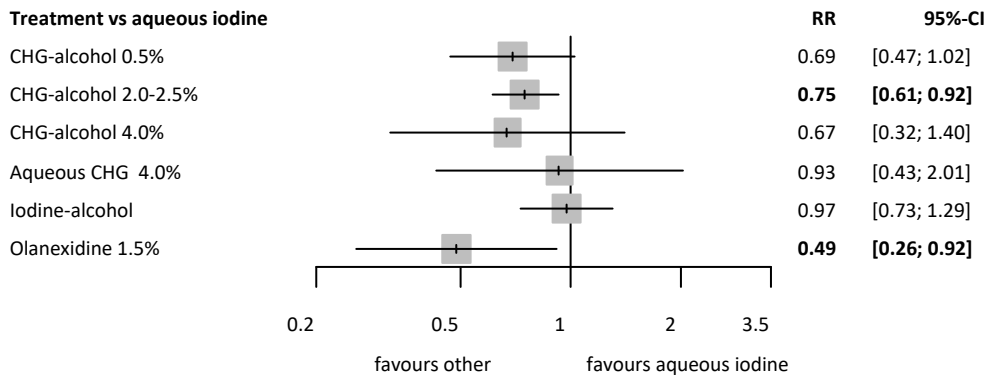
1.9 CHG-alcohol 2.0-2.5% versus Iodine-alcohol

Five studies (n=3792) contributed with a direct comparison to the NMA investigating the effect of CHG-alcohol 0.5% versus Iodine-alcohol on SSI (Ritter, 2020; Broach, 2017; Xu, 2017; Tuuli, 2016; Ngai, 2015). Two studies (Savage, 2012; Saltzman, 2009) reported no SSI in both arms and were thus excluded from the NMA. The overall network RR was 0.77 (95% CI 0.60, 1.00), a non-significant but clinically relevant difference favoring CHG-alcohol 2.0-2.5%.

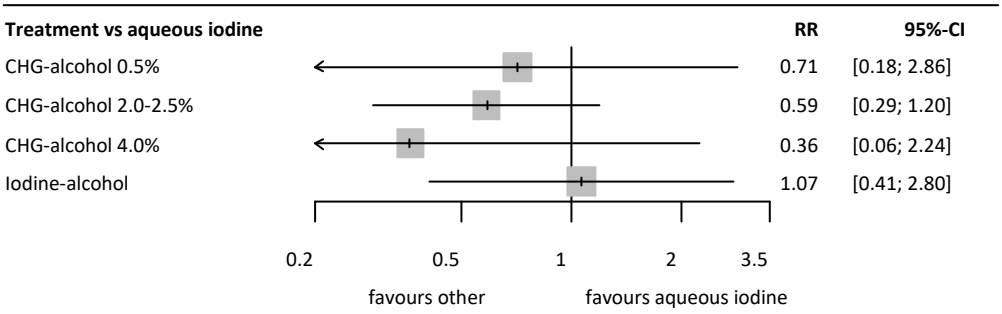
1.10 Results NMA

Results from the NMA are presented in de forest plots shown in Figure 2 and 3.

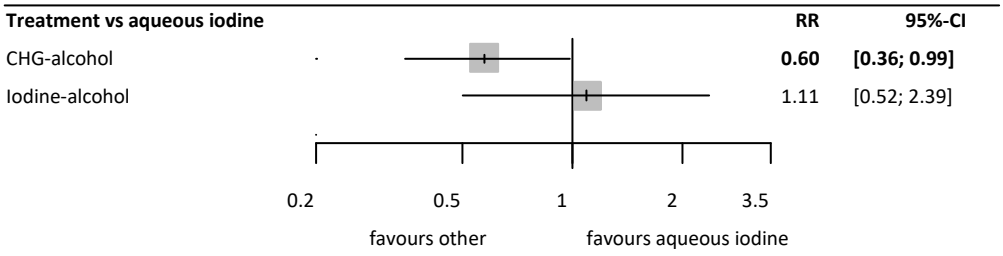
A. Any type of surgery



B. CDC wound classification 1 (clean surgery)



C. CDC wound classification 1 (clean surgery)



D. Non-clean surgery

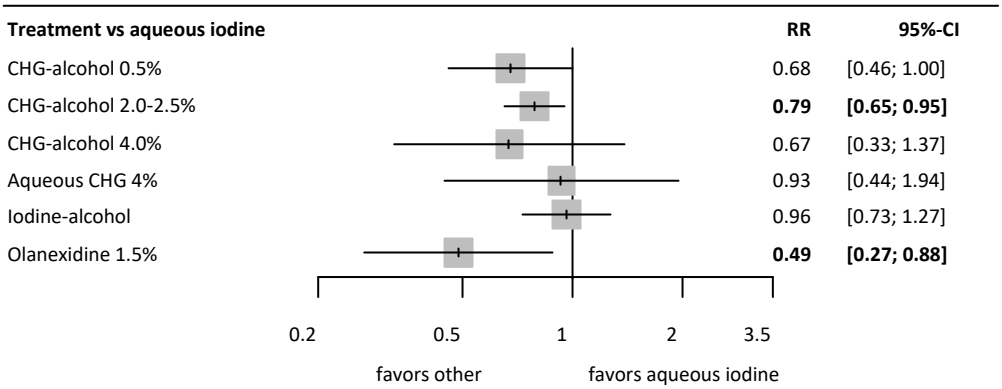
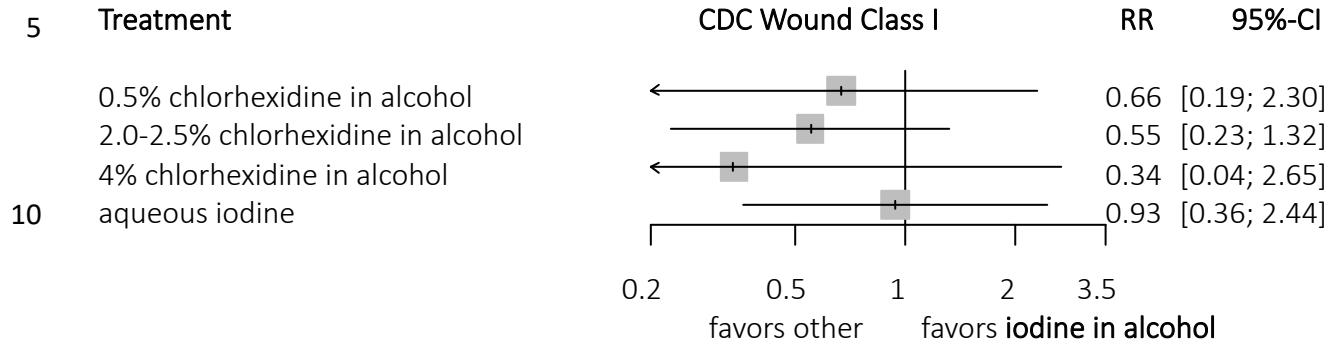


Figure 2. Forest plots

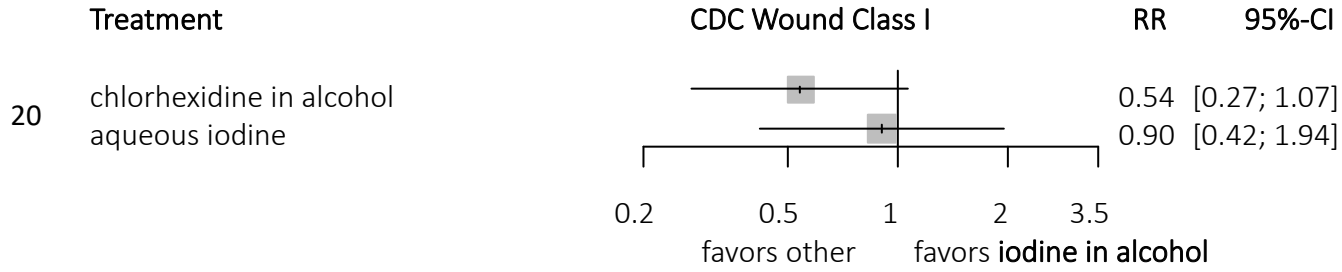
The forest plots show the efficacy of different skin preparation solutions and concentrations in the prevention of SSIs compared with aqueous iodine. Data are RR with corresponding 95% CI. (A) Efficacy for any type of surgery. (B) Efficacy for clean surgery. (C) Efficacy for clean surgery, clustering of chlorhexidine in alcohol. (D) Efficacy for non-clean surgery, excluding studies looking only at clean surgical procedures (ie. only wound class 1).

Figure3. Forest plots

3a. Compared with iodine in alcohol (clean surgery).



3b. Compared with iodine in alcohol (clean surgery), clustering of CHG-alcohol.



2. Adverse events

Since the number of events does not meet the optimal information size, we did not grade the body of evidence for the outcome adverse events. However, since it may hold important clinical information, the type of adverse skin events is presented across the different interventions in table 1. Adverse events of the skin related to the skin preparation solutions were mentioned in 10 RCTs (NIHR, 2021; Obara, 2020; Broach, 2017; Park, 2017; Tuuli, 2016; Bibi, 2015; Srinivas, 2015; Yeung, 2013; Darouiche, 2010; Paocharoen, 2009). Five studies (NIHR, 2021; Broach, 2017; Park, 2017; Srinivas, 2015; Yeung, 2013) reported no adverse events, the other five studies reported a total of 59 mild adverse events, mainly erythema, pruritus, dermatitis, skin irritation or mild allergic symptoms. None of the RCTs found a significant difference in adverse events in the groups. The results are depicted in table 1.

Table 1. Number of adverse skins events related to study medication

Study	Comparison	Adverse skin events related to study medication
NIHR 2020	CHG-alcohol 2.0%	No events
	Aqueous iodine 1% AI	No events
Obara 2020	Aqueous iodine 1% AI	5 patients with erythema, pruritus or dermatitis
	Olanexidine 1.5%	5 patients with erythema, pruritus or dermatitis
Broach 2017	CHG-alcohol 2.0%	No events
	Iodine-alcohol 0.7% AI	No events
Park 2017	CHG-alcohol 4.0%	No events
	Aqueous iodine 1% AI	No events
Tuuli 2016	CHG-alcohol 2.0%	17 patients with adverse skin reactions with erythema at operative site, allergic skin reaction or skin irritation or allergic skin reaction
	Iodine-alcohol 0.7% AI	19 patients with erythema at operative site, skin irritation, allergic skin reaction or skin irritation or allergic skin reaction

Bibi 2015	CHG-alcohol 2.0%	No events
	Aqueous iodine 1% AI	2 patients with mild allergic symptoms
Srinivas 2015	CHG-alcohol 0.5%	No events
	Aqueous iodine 0.5% AI	No events
Yeung 2013	CHG-alcohol 2.0%	No events
	Aqueous iodine 1% AI	No events
Darouiche 2010	CHG-alcohol 2.0%	3 patients with pruritus, erythema, or both around the surgical wound
	Aqueous iodine 1% AI	3 patients with pruritus, erythema, or both around the surgical wound
Paocharoen 2009	CHG-alcohol 4.0%	No events
	Aqueous iodine 1% AI	2 patients with skin irritation

Level of evidence of the literature

The GRADE approach for rating the certainty of estimates of treatment effects was used. Since all included studies are randomized controlled trials, the rating for the GRADE starts high for all comparisons. Each comparison can be downgraded due to one of the following reasons:

- **Risk of bias:** Of the 27 studies included in the network meta-analysis, six had an overall "High risk of bias". Due to the network meta-analysis, this may influence all the network estimates of all comparison. We performed a (network) sensitivity meta-analysis excluding studies with high risk of bias. The results were comparable with the overall analysis, and downgrading for risk of bias was not needed.*
- **Inconsistency:** When comparing the effect estimates of the direct and indirect results after netsplitting, we see consistency over all comparisons (Appendix 6)
- **Imprecision:** For relative risks that cross the null-effect threshold (RR 1) we downgraded with one. If the threshold is not crossed, we did not downgrade. The only exception to this is the comparison Olanexidine 1.5% versus aqueous iodine. We see a large effect that does not cross the threshold. However, the optimal information size is not met (based on one RCT),47 which results in -1 downgrade for imprecision.
- **Publication bias:** The comparison-adjusted funnel plot showed no sign of small-study effects (see funnel plot).

* *Of the 27 studies included in the NMA, six had an overall "High risk of bias". Due to the nature of a NMA, this may influence all the network estimates of all comparisons. In a sensitivity analysis excluding studies with high risk of bias the results were comparable with the main analysis, thus downgrading for risk of bias was not needed. In addition, some comparisons were also downgraded because of imprecision. Overall, the certainty of the treatments effects was deemed moderate, except for one comparison, which was deemed high (CHG 2.0-2.5% vs aqueous iodine).*

Table 2. Level of evidence per comparison for the outcome surgical site infections

Comparison	Reasons for downgrading		
	Direct evidence	**Indirect evidence**	**Network meta-analysis**
CHG-alcohol 0.5% vs. CHG-alcohol 2.0-2.5%	-1 imprecision	-1 imprecision	-1 imprecision
CHG-alcohol 0.5% vs. CHG-alcohol 4.0%	-	-1 imprecision	-1 imprecision
CHG-alcohol 0.5% vs. aqueous CHG 4.0%	-	-1 imprecision	-1 imprecision
CHG-alcohol 0.5% vs. aqueous iodine	-1 imprecision	-1 imprecision	-1 imprecision
CHG-alcohol 0.5% vs. iodine-alcohol	-1 imprecision	-1 imprecision	-1 imprecision
CHG-alcohol 0.5% vs. olanexidine 1.5%	-	-1 imprecision	-1 imprecision
CHG-alcohol 2.0-2.5% vs. CHG-alcohol 4.0%	-	-1 imprecision	-1 imprecision
CHG-alcohol 2.0-2.5% vs. aqueous CHG 4.0%	-	-1 imprecision	-1 imprecision
CHG-alcohol 2.0-2.5% vs. aqueous iodine	-1 imprecision	-1 imprecision	-1 imprecision

CHG-alcohol 2.0-2.5% vs. iodine-alcohol	No downgrade	-1 imprecision	No downgrade
CHG-alcohol 2.0-2.5% vs. olanexidine 1.5%	-	-1 imprecision	-1 imprecision
CHG-alcohol 4.0% vs aqueous CHG 4.0%	-	-1 imprecision	-1 imprecision
CHG-alcohol 4.0% vs. aqueous iodine	-1 imprecision	-	-1 imprecision
CHG-alcohol 4.0% vs. iodine-alcohol	-	-1 imprecision	-1 imprecision
CHG-alcohol 4.0% vs. olanexidine 1.5%	-	-1 imprecision	-1 imprecision
Aqueous CHG 4.0% vs. aqueous iodine	-1 imprecision	-	-1 imprecision
Aqueous 4.0% vs. iodine-alcohol	-	-1 imprecision	-1 imprecision
Aqueous 4.0% vs. olanexidine 1.5%	-	-1 imprecision	-1 imprecision
Aqueous iodine vs. iodine-alcohol	-1 imprecision	-1 imprecision	-1 imprecision
Aqueous iodine vs. olanexidine 1.5%	-1 imprecision	-	-1 imprecision
Iodine-alcohol vs. olanexidine 1.5%	-	-1 imprecision	-1 imprecision

If only direct or indirect evidence is available for a given comparison, the network quality rating will be based on that estimate. When, for a particular comparison, both direct and indirect evidence are available, we used the highest of the two quality ratings as the quality rating for the NMA estimate. The quality of the network estimate can be upgraded if precision is greater than direct or indirect estimates.

Table 3. GRADE table

Comparison	Direct evidence		Indirect evidence		Network meta-analysis	
	Relative Risk (95%CI)	Certainty of evidence	Relative Risk (95%CI)	Certainty of evidence	Relative Risk (95%CI)	Certainty of evidence
CHG-alcohol 0.5% vs. CHG-alcohol 2.0-2.5%	3.00 (0.61 - 14.74)	⊕⊕⊕O moderate	0.83 (0.54 - 1.29)	⊕⊕⊕O moderate	0.93 (0.60 - 1.43)	⊕⊕⊕O moderate
CHG-alcohol 0.5% vs. CHG-alcohol 4.0%	-	-	1.04 (0.45 - 2.39)	⊕⊕⊕O moderate	1.04 (0.45 - 2.39)	⊕⊕⊕O moderate
CHG-alcohol 0.5% vs. aqueous CHG 4.0%	-	-	0.74 (0.31 - 1.79)	⊕⊕⊕O moderate	0.74 (0.31 - 1.79)	⊕⊕⊕O moderate
CHG-alcohol 0.5% vs. aqueous iodine	0.68 (0.45 - 1.03)	⊕⊕⊕O moderate	0.78 (0.26 - 2.38)	⊕⊕⊕O moderate	0.69 (0.47 - 1.02)	⊕⊕⊕O moderate
CHG-alcohol 0.5% vs. iodine-alcohol	0.33 (0.08 - 1.44)	⊕⊕⊕O moderate	0.78 (0.47 - 1.29)	⊕⊕⊕O moderate	0.71 (0.45 - 1.14)	⊕⊕⊕O moderate
CHG-alcohol 0.5% vs. olanexidine 1.5%	-	-	1.43 (0.68 - 3.01)	⊕⊕⊕O moderate	1.43 (0.68 - 3.01)	⊕⊕⊕O moderate
CHG-alcohol 2.0-2.5% vs. CHG-alcohol 4.0%	-	-	1.12 (0.52 - 2.41)	⊕⊕⊕O moderate	1.12 (0.52 - 2.41)	⊕⊕⊕O moderate
CHG-alcohol 2.0-2.5% vs. aqueous CHG 4.0%	-	-	0.81 (0.36 - 1.79)	⊕⊕⊕O moderate	0.81 (0.36 - 1.79)	⊕⊕⊕O moderate
CHG-alcohol 2.0-2.5% vs. aqueous iodine	**0.77 (0.62 - 0.97)**	⊕⊕⊕⊕ high	0.62 (0.36 - 1.06)	⊕⊕⊕O moderate	**0.75 (0.61 - 0.92)**	⊕⊕⊕⊕ high

CHG-alcohol 2.0-2.5% vs. iodine-alcohol	0.76 (0.57 - 1.03)	⊕⊕⊕O moderate	0.78 (0.46 - 1.34)	⊕⊕⊕O moderate	0.77 (0.60 - 1.00)	⊕⊕⊕O moderate
CHG-alcohol 2.0-2.5% vs. olanexidine 1.5%	-	-	1.54 (0.79 - 3.00)	⊕⊕⊕O moderate	1.54 (0.79 - 3.00)	⊕⊕⊕O moderate
CHG-alcohol 4.0% vs. aqueous CHG 4.0%	-	-	0.71 (0.25 - 2.08)	⊕⊕⊕O moderate	0.71 (0.25 - 2.08)	⊕⊕⊕O moderate
CHG-alcohol 4.0% vs. aqueous iodine	0.77 (0.32 - 1.41)	⊕⊕⊕O moderate	-	-	0.77 (0.32 - 1.41)	⊕⊕⊕O moderate
CHG-alcohol 4.0% vs. iodine-alcohol	-	-	0.69 (0.31 - 1.53)	⊕⊕⊕O moderate	0.69 (0.31 - 1.53)	⊕⊕⊕O moderate
CHG-alcohol 4.0% vs. olanexidine 1.5%	-	-	1.38 (0.52 - 3.65)	⊕⊕⊕O moderate	1.38 (0.52 - 3.65)	⊕⊕⊕O moderate
Aqueous CHG 4.0% vs. aqueous iodine	0.93 (0.43 - 2.01)	⊕⊕⊕O moderate	-	-	0.93 (0.43 - 2.01)	⊕⊕⊕O moderate
Aqueous CHG 4.0% vs. iodine-alcohol	-	-	0.96 (0.42 - 2.19)	⊕⊕⊕O moderate	0.96 (0.42 - 2.19)	⊕⊕⊕O moderate
Aqueous CHG 4.0% vs. olanexidine 1.5%	-	-	1.91 0.70 - 5.20)	⊕⊕⊕O moderate	1.91 0.70 - 5.20)	⊕⊕⊕O moderate
Iodine-alcohol vs. aqueous iodine	0.86 (0.53 - 1.39)	⊕⊕⊕O moderate	1.04 (0.71 - 1.52)	⊕⊕⊕O moderate	0.97 (0.72 - 1.30)	⊕⊕⊕O moderate
Olanexidine 1.5% vs. aqueous iodine	**0.49 (0.26 - 0.92)**	⊕⊕⊕O moderate	-	**-**	**0.49 (0.26 - 0.92)**	⊕⊕⊕O moderate
Iodine-alcohol vs. olanexidine 1.5%	.	-	2.00 (0.99 - 4.00)	⊕⊕⊕O moderate	2.00 (0.99 - 4.00)	⊕⊕⊕O moderate

Conclusions

Surgical site infections (SSI)

CHG-alcohol 0.5% vs. CHG-alcohol 2.0-2.5%

Moderate GRADE	CHG-alcohol 0.5% likely results in little to no difference on SSI when compared with CHG-alcohol 2.0-2.5% in surgical patients.

CHG-alcohol 0.5% vs. CHG-alcohol 4.0%

Moderate GRADE	CHG-alcohol 0.5% likely results in little to no difference on SSI when compared with CHG-alcohol 4.0% in surgical patients.

CHG-alcohol 0.5% vs. aqueous CHG 4.0%

Moderate GRADE	CHG-alcohol 0.5% likely reduces SSI when compared with aqueous CHG 4.0% in surgical patients.

CHG-alcohol 0.5% vs. aqueous iodine

Moderate GRADE	CHG-alcohol 0.5% likely reduces SSI when compared with aqueous iodine in surgical patients.

CHG-alcohol 0.5% vs. iodine-alcohol

Moderate GRADE	CHG-alcohol 0.5% likely reduces SSI when compared with iodine-alcohol in surgical patients.

CHG-alcohol 0.5% vs. olanexidine 1.5%

Moderate GRADE	CHG-alcohol 0.5% likely increases SSI when compared with olanexidine 1.5% in surgical patients.

CHG-alcohol 2.0-2.5% vs. CHG-alcohol 4.0%

Moderate GRADE	CHG-alcohol 2% likely results in little to no difference on SSI when compared with CHG-alcohol 4.0% in surgical patients.

CHG-alcohol 2.0-2.5% vs. aqueous CHG 4.0%

Moderate GRADE	CHG-alcohol 2% likely results in little to no difference on SSI when compared with aqueous CHG 4.0% in surgical patients, but the evidence is very uncertain.

CHG-alcohol 2.0-2.5% vs. aqueous iodine

High GRADE	CHG-alcohol 2.0-2.5% results in a reduction of SSI when compared with aqueous iodine in surgical patients.

CHG-alcohol 2.0-2.5% vs. iodine-alcohol

Moderate GRADE	CHG-alcohol 2.0-2.5% likely reduces SSI when compared with iodine-alcohol in surgical patients.

CHG-alcohol 2.0-2.5% vs. olanexidine 1.5%

Moderate GRADE	CHG-alcohol 2.0-2.5% likely increases SSI when compared with olanexidine 1.5% in surgical patients.

CHG-alcohol 4.0% vs. aqueous CHG 4.0%

Moderate GRADE	CHG-alcohol 4.0% likely reduces SSI when compared with aqueous CHG 4.0% in surgical patients.

CHG-alcohol 4.0% vs. aqueous iodine

Moderate GRADE	CHG-alcohol 4.0% likely reduces SSI when compared with aqueous iodine in surgical patients.

CHG-alcohol 4.0% vs. iodine-alcohol

Moderate GRADE	CHG 4.0% likely reduces SSI when compared with iodine-alcohol in surgical patients.

CHG-alcohol 4.0% vs. olanexidine 1.5%

Moderate GRADE	CHG-alcohol 4.0% likely increases SSI when compared with olanexidine 1.5% in surgical patients.

Aqueous CHG 4.0% vs. aqueous iodine

Moderate GRADE	CHG 4.0% likely results in little to no difference on SSI when compared with aqueous iodine in surgical patients.

Aqueous CHG 4.0% vs. iodine-alcohol

Moderate GRADE	CHG 4.0% likely results in little to no difference on SSI when compared with iodine-alcohol in surgical patients.

Aqueous CHG 4.0% vs. olanexidine 1.5%

Moderate GRADE	CHG 4.0% likely increases SSI when compared with olanexidine 1.5% in surgical patients.

Aqueous iodine vs. iodine-alcohol

Moderate GRADE	Aqueous iodine likely results in little to no difference on SSI when compared with iodine-alcohol in surgical patients.

Aqueous iodine vs. olanexidine 1.5%

Moderate GRADE	Aqueous iodine likely increases SSI when compared with olanexidine 1.5% in surgical patients.

Iodine-alcohol vs. olanexidine 1.5%

Moderate GRADE	Iodine-alcohol likely increases SSI when compared with olanexidine 1.5% in surgical patients.

Considerations - Evidence to decision

Summary of the evidence

There is a benefit of the use of either 2.0-2.5% CHG-alcohol or 1.5% olanexidine (evidence from only one RCT) in the reduction of SSI compared with aqueous iodine in any type of surgery. The results of 0.5% CHG-alcohol and 4.0% CHG-alcohol also suggests a beneficial effect but remain non-significant with a wide confidence interval. This may be due to limited evidence for 0.5% CHG-alcohol and 4.0% CHG-alcohol. Aqueous CHG and iodine-alcohol showed comparable effects compared to aqueous iodine. Olanexidine, a new antiseptic solution, was found to be most effective, but, due to its novelty, investigated in only one RCT.

Incidence SSI

An overall SSI rate of 12,1% was found, which is high compared to recent literature on SSI rate across all surgery. This can be explained by the 20% SSI rate reported by the largest included RCT undertaken in seven low-income and middle-income countries. NIHR 2021 *et al.* reported 1163 (20,1%) SSI in 5788 patients undergoing abdominal surgery (CDC wound classification II, III or IV) with a skin incision of five centimeter or greater. Without this RCT, all other included studies report a total number of 981 SSI in 11,947 patients (8,2%).

The overall level of evidence for the outcome SSI was graded as moderate (downgraded because of imprecision) and in one comparison high.

Adverse events

The potential adverse effects were also investigated. Only ten of the 33 included studies reported adverse skin reactions, with five of the studies reporting actual events. These individual studies found no substantial difference in the incidence of adverse events between

the different antiseptic solutions. Although there is evidence suggesting a high concentration (4.0%) of CHG-alcohol should be avoided since it is known to be irritant in high concentrations, the evidence was too scarce to analyse this properly.

Subgroup: clean surgery

In clean surgery only, a potential benefit of the different concentrations CHG-alcohol over aqueous iodine is found. These effects were not significant due to a wide confidence interval, possibly because of the low incidence of SSI and a relatively small number of patients. The incidence of SSI in clean surgery only studies was 4.8 % (158 SSI in 3301 patients), whereas after excluding these studies, the incidence of SSI was 13.1% (2044 SSI in 15,562 patients) for non-clean surgery. When clustering the different concentrations of CHG-alcohol into one group CHG-alcohol is significantly more effective than aqueous iodine. Compared to iodine-alcohol, clustering CHG-alcohol shows a benefit, however this remains non-significant (figure 3a and figure 3b).

It could be assumed that skin antisepsis would be equally effective in clean and non-clean surgery when SSI only originates from the skin. However, in non-clean surgery, spillage from contaminated surgical areas to the wound surface, wound edges and surrounding skin also plays a role. Antiseptics are toxic to bacteria and therefore aid their mechanical removal. Alcohol-based antiseptic solutions have durable effects more than six hours after skin preparation with broader spectrum antimicrobial activity after surgical spillage.

International guidelines

In contrast to previous international recommendations, 2.0-2.5% CHG-alcohol was found to be superior to other concentrations of CHG-alcohol. The US Centers for Disease Control and Prevention (Berrios-Torres 2017) advises alcohol-based solutions, whereas the National Institute for Health and Care Excellence (NICE 2019) and World Health Organisation guidelines (WHO 2018) recommend explicitly CHG in alcohol as antiseptic for reduction of SSI. Since publication of these guidelines, many new RCTs have been conducted investigating various types of antiseptic solutions. In this guideline, seven additional studies were added compared to the NICE guideline, all published since 2019; and eleven additional studies compared to the WHO guideline since 2016.

Here, we focus on skin preparation, however, one should understand that it is not the only preventative measure for SSI. Other measures, such as timing and dosing of surgical antimicrobial prophylaxis, normovolemia, irrigation of operative wound, etc., are of equal importance. Most of the included studies adhere to best practice guidelines, but not all studies included in the literature mentioned this, and heterogeneity of other preventative measures are inevitable.

Patient preferences

There are no patient preferences regarding the included skin preparation solutions, since none of the described preparation methods showed increased risk of skin irritation or other harmful effects on patient-related outcomes.

Resource use

There are no cost-effective studies available. However, SSI is a costly complication and therefore, the prevention of SSI contributes more to cost reduction than the difference in costs between individual antiseptic solutions.

Sustainability, feasibility, and implementation

There are no issues regarding to the feasibility of the different skin preparation solutions for implementation in clinical practice.

Recommendations

Rationale of the recommendation

There is a benefit of all different CHG-alcohol concentrations over iodine in the prevention of SSI, in adult patients undergoing surgical procedures, in particular 2.0-2.5% CHG-alcohol. However, no difference of effectiveness is found between different concentrations of CHG-alcohol for clean surgery. Although, when clustering the different concentrations into one group a benefit is seen over aqueous iodine. Olanexidine 1.5% also shows a potential benefit over iodine in the prevention of SSI in clean-contaminated surgery, though this is based on one single randomised trial and further investigation is needed.

Gebruik voorafgaand aan chirurgische interventies 2.0-2.5% chloorhexidine-alcohol voor het desinfecteren van de huid van de patiënt, ter preventie van postoperatieve wondinfecties.

- *Voor schone chirurgische interventies kan geen specifieke concentratie chloorhexidine-alcohol worden aanbevolen.*

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