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Effectiveness of antibacterial therapeutic clothing vs. nonantibacterial therapeutic clothing in patients with moderate-to-severe atopic dermatitis: a randomized controlled observer-blind pragmatic trial (ABC trial)

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Abstract

Background Increased *Staphylococcus aureus* (SA) colonization is considered an important factor in the pathogenesis of atopic dermatitis (AD). Antibacterial therapeutic clothing aims to reduce SA colonization and AD inflammation; however, its role in the management of AD remains poorly understood.

Objectives To investigate the effectiveness of antibacterial therapeutic clothing + standard topical treatment in patients with moderate-to-severe AD vs. standard therapeutic clothing + standard topical treatment; and, if effectiveness was demonstrated, to demonstrate its cost-effectiveness.

Methods A pragmatic double-blinded multicentre randomized controlled trial (NCT04297215) was conducted in patients of all ages with moderate-to-severe AD. Patients were centrally randomized 1 : 1 : 1 to receive standard therapeutic clothing or antibacterial clothing based on chitosan or silver. The primary outcome was the between-group difference in Eczema Area and Severity Index (EASI) measured over 52 weeks. Secondary outcomes included patient-reported outcomes (PROs), topical corticosteroid (TCS) use, SA colonization, safety and cost-effectiveness. Outcomes were assessed by means of (generalized) linear mixed-model analyses.

Results Between 16 March 2020 and 20 December 2021, 171 patients were enrolled. In total, 159 patients were included (54 in the standard therapeutic clothing group, 50 in the chitosan group and 55 in the silver group). Adherence was high [median 7 nights a week wear (interquartile range 3–7)]. Median EASI scores at baseline and at 4, 12, 26 and 52 weeks were 11.8, 4.3, 4.6, 4.2 and 3.6, respectively, in the standard therapeutic clothing group vs. 11.3, 5.0, 3.0, 3.0 and 4.4, respectively, in the chitosan group, and 11.6, 5.0, 5.4, 4.6 and 5.8, respectively, in the silver group. No differences in EASI over 52 weeks between the standard therapeutic clothing group, the chitosan group [–0.1, 95% confidence interval (CI) –0.3 to 0.2; $P=0.53$] or the silver group (–0.1, 95% CI –0.3 to 0.2; $P=0.58$) were found. However, a small significant group × time interaction effect between the standard and silver groups was found ($P=0.03$), in which the silver group performed worse after 26 weeks. No differences between groups were found in PROs, TCS use, SA skin colonization and healthcare utilization. No severe adverse events or silver absorption were observed.

Conclusions The results of this study suggest no additional benefits of antibacterial agents in therapeutic clothing in patients with moderate-to-severe AD.

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What is already known about this topic?

- Evidence on the effectiveness of antibacterial therapeutic clothing in the management of moderate-to-severe atopic dermatitis (AD) is limited.

What does this study add?

- This study showed no superiority of antibacterial therapeutic clothing in terms of alleviating AD severity and symptoms, improving quality of life, reducing topical corticosteroid use, suppressing *Staphylococcus aureus* skin colonization or lowering healthcare utilization if used in addition to topical treatment in patients with moderate-to-severe AD.
- The use of therapeutic clothing in AD is safe.

Atopic dermatitis (AD) is a prevalent chronic inflammatory skin disorder.[1] AD is characterized by intense pruritus and recurrent eczematous skin lesions. AD can have a considerable impact on the quality of life (QoL) of patients and their families.[2] The basic treatment of AD consists of emollients and topical anti-inflammatory treatment.[3] Although basic treatment can be sufficient for patients with mild AD, many patients with moderate and severe AD do not achieve disease control with topical treatment alone.[4] In the past, special clothing and bandages have been used as part of AD treatment, to protect the skin from further damage through scratching and other irritating factors.[5]

In the Netherlands, therapeutic clothing with antibacterial agents such as chitosan and silver was introduced in 2000.[6] Prior studies have demonstrated the antibacterial properties of these agents in healthcare.[7,8] Increased colonization with *Staphylococcus aureus* (SA) has been observed in patients with AD and has been speculated to influence AD severity by interaction with the skin barrier and immune system.[9] By reducing SA colonization, antibacterial therapeutic clothing aims to reduce AD symptoms and achieve more disease control. However, studies that have investigated (antibacterial) therapeutic clothing are scarce.[6] Based on the positive experiences of patients and clinicians, antibacterial therapeutic clothing was recommended in the Dutch AD guidelines for patients with moderate-to-severe AD who are unable to taper topical corticosteroids (TCS).[6] In 2015 the Dutch National Healthcare Institute, evaluated the effectiveness of antibacterial therapeutic clothing and concluded that there was insufficient evidence for the effectiveness of antibacterial therapeutic clothing and ended its reimbursement.[10] At the request of patients and professionals, the Dutch Ministry of Health, Welfare and Sport facilitated a trial to investigate the added benefit of antibacterial therapeutic clothing in patients with moderate-to-severe AD vs. standard therapeutic clothing and, if found to be effective, the cost-effectiveness of antibacterial clothing.[11]

Materials and methods

Study design

This 1-year multicentre parallel group double-blind pragmatic randomized controlled trial (NCT04297215) was conducted at five hospitals in the Netherlands. Participants were randomized to receive therapeutic clothing + standard AD care; antibacterial therapeutic clothing based on chitosan + standard care; or antibacterial clothing based on silver + standard care. The primary outcome – AD severity – was assessed at baseline and at 4, 12, 26 and 52 weeks. This study included a cost-effectiveness component. The detailed study protocol has been published previously.[11]

Recruitment

Recruitment took place at four Dutch academic medical centres (Erasmus MC University Medical Center, Amsterdam University Medical Centers, University Medical Center Utrecht and University Medical Center Groningen) and one regional hospital (St. Antonius Hospital, Nieuwegein). Potential participants were identified through primary and secondary care, the patient organization for those with AD (VMCE) and via a media advertisement.

Patients of all ages were eligible for participation if they had AD according to the UK Working Party's Diagnostic Criteria;[12] and moderate-to-severe AD expressed as an Eczema Area and Severity Index (EASI) score $\geq$ 6 at baseline.[13,14] Key exclusion criteria were the use of systemic immunosuppressive agents, antibiotics, phototherapy, (antibacterial) therapeutic clothing for AD within 1 month before baseline and the use of topical antibiotics until 1 week before baseline. The complete list of inclusion and exclusion criteria are listed in Appendix S1 (see Supporting Information).

Randomization, blinding and allocation concealment

Patients were randomly assigned (1 : 1 : 1) to standard therapeutic clothing, antibacterial therapeutic clothing based on chitosan or antibacterial therapeutic clothing based on silver, stratified by baseline AD severity [moderate (EASI 6.0–22.9) vs. severe (EASI 23.0–72.0)][14] and age (0–5, 6–17 and $\geq$ 18 years). Blinded assessors were unaware of the treatment allocation until the completion of all study procedures. Therapeutic clothing, without brand names and labels to ensure allocation concealment, was shipped directly to patients by a third party. However, minor colour differences between the three types of clothing could not be adjusted. Detailed information on the randomization and blinding procedure is provided in Appendix S2 (see Supporting Information).

Procedures

All therapeutic clothing used in this study were licensed with a CE mark as a medical device for AD. To increase the generalizability of our findings, two types of antibacterial therapeutic clothing were included. The control group received Binamed® therapeutic clothing without antibacterial agents (BAP Medical, Apeldoorn, the Netherlands), made of micromodal and LYCRA®. Micromodal is a semi-synthetic wood cellulose fibre. This fibre has a high strength and elasticity, and high moisture permeability. The intervention groups received either DermaCura® antibacterial clothing (D&M, Zeist, the Netherlands) or Binamed antibacterial therapeutic clothing (BAP Medical). DermaCura antibacterial clothing (D&M) is made from 98% TENCEL™ and 2% elastane. Chitosan (1%) is added to the TENCEL. Binamed antibacterial therapeutic clothing (BAP Medical) consists of micromodal LYCRA and woven silver filaments.

At the beginning of the study, the patients received three sets of therapeutic clothing and standardized instructions. During the study, patients could request three additional sets of therapeutic clothing. Each set consisted of a long-sleeved shirt and full-length leggings. Socks and gloves were prescribed when deemed necessary by the treating physician. Patients were instructed to wear the clothing at least overnight. During the study, basic care (emollients, TCS, topical calcineurin inhibitors and/or antihistamines) was continued according to Dutch AD guidelines.[15] In the case of severe exacerbation requiring ultraviolet therapy, systemic antibiotics or systemic treatment with immunosuppressive medication, participation in the study was stopped.

Outcomes

All core outcomes, as defined by the Harmonising Outcome Measures for Eczema (HOME) initiative, were included.[16] A full overview and description of all outcomes is provided in Appendixes S3 and S4 (see Supporting Information).

Primary outcome

The primary outcome – AD severity – was assessed using the EASI.[13] Blinded investigators assessed EASI score at baseline, and at 4, 12, 26 and 52 weeks of follow-up. The EASI evaluates AD severity based on the evaluation of four clinical signs (erythema, excoriation, oedema/papulation and lichenification) and assessment of the affected area in each body region (head and neck, upper limbs, lower limbs and trunk). EASI scores range from 0 to 72, with higher scores indicating more severe AD.

Secondary outcomes

Secondary outcomes included (i) Investigator Global Assessment (IGA);[17] (ii) IGA impetiginization;[18] (iii) Patient Oriented Eczema Measure (POEM);[19] (iv) numerical rating scale for peak pruritus over the past 24 h;[20] (v) QoL, as measured by the Dermatology Life Quality Index (DLQI) in adults,[21] the Children's DLQI (CDLQI)[22] in children aged 4–16 and the Infants' Dermatitis Quality of Life Index (IDQOL) in infants (aged <4 years);[23] (vi) Recap of atopic eczema (RECAP);[24] (vii) TCS potency class (based on Anatomical Therapeutic Classification of the World Health Organization);[25] (viii) number of TCS application days per week (Appendix S5; see Supporting Information); (ix) estimated duration of use of a standard 30-g tube of TCS (Appendix S6; see Supporting Information); (x) SA skin colonization; and (xi) AD-related costs.

Safety outcomes

Adverse events (AEs) possibly related to therapeutic clothing, skin-related AEs, serious AEs and urinary silver concentration were assessed over the 52-week follow-up period (Appendix S7; see Supporting Information).

Statistical analysis

Analyses were carried out in spss statistics (version 28; IBM, Armonk, NY, USA) and r (version 4.2; R Foundation for Statistical Computing, Vienna, Austria). The main approach to the analyses was intention to treat, regardless of adherence to therapeutic clothing, and included patients who provided data for at least one timepoint. (Generalized) linear mixed-effects models were used to evaluate primary and secondary outcomes with group, time, outcome at baseline and time $\times$ group as independent variables. Time was defined as a continuous variable and a two-sided alpha of 0.05 was used. No multiplicity adjustment was made. In these analyses, both types of antibacterial therapeutic clothing were independently investigated against the standard therapeutic clothing group. Our primary endpoint for each analysis was the between-group difference over 52 weeks of follow-up. For sample size calculation, we used a SD of 13 and minimal important change (MIC) for the EASI of 6.6, resulting in a medium Cohen's d effect size of 0.51 for the overall difference between groups. The MIC was chosen as effect size, in order to reflect a clinically meaningful difference. Considering a power of 0.80, three groups, five measurement periods, a 0.6 EASI score correlation and a 20% dropout rate, we aimed to recruit 55 patients per group, totalling 165 participants. Refer to Appendixes S8 and S9 for additional information (see Supporting Information).

Results

Baseline characteristics

In total, 171 patients were randomized between March 2020 and December 2021 (the last study visit was completed in December 2022). After randomization, four patients were lost due to a COVID-19 infection, withdrawal of consent or loss to follow-up. These patients did not complete the baseline visit. The remaining 167 patients participated in the trial. Of these patients, eight were inappropriately randomized owing to incorrect calculation of EASI score, resulting in a failure to meet the inclusion criteria and were therefore excluded from the analyses. In total, 159 patients were included in the analyses (Figure 1). The baseline characteristics of the patients included in the analyses are presented in Table 1. Median age was 8 [interquartile range (IQR) 3–24] years and median EASI score was 11.6 (IQR 8.4–16.8). The baseline demographic and clinical characteristics of the

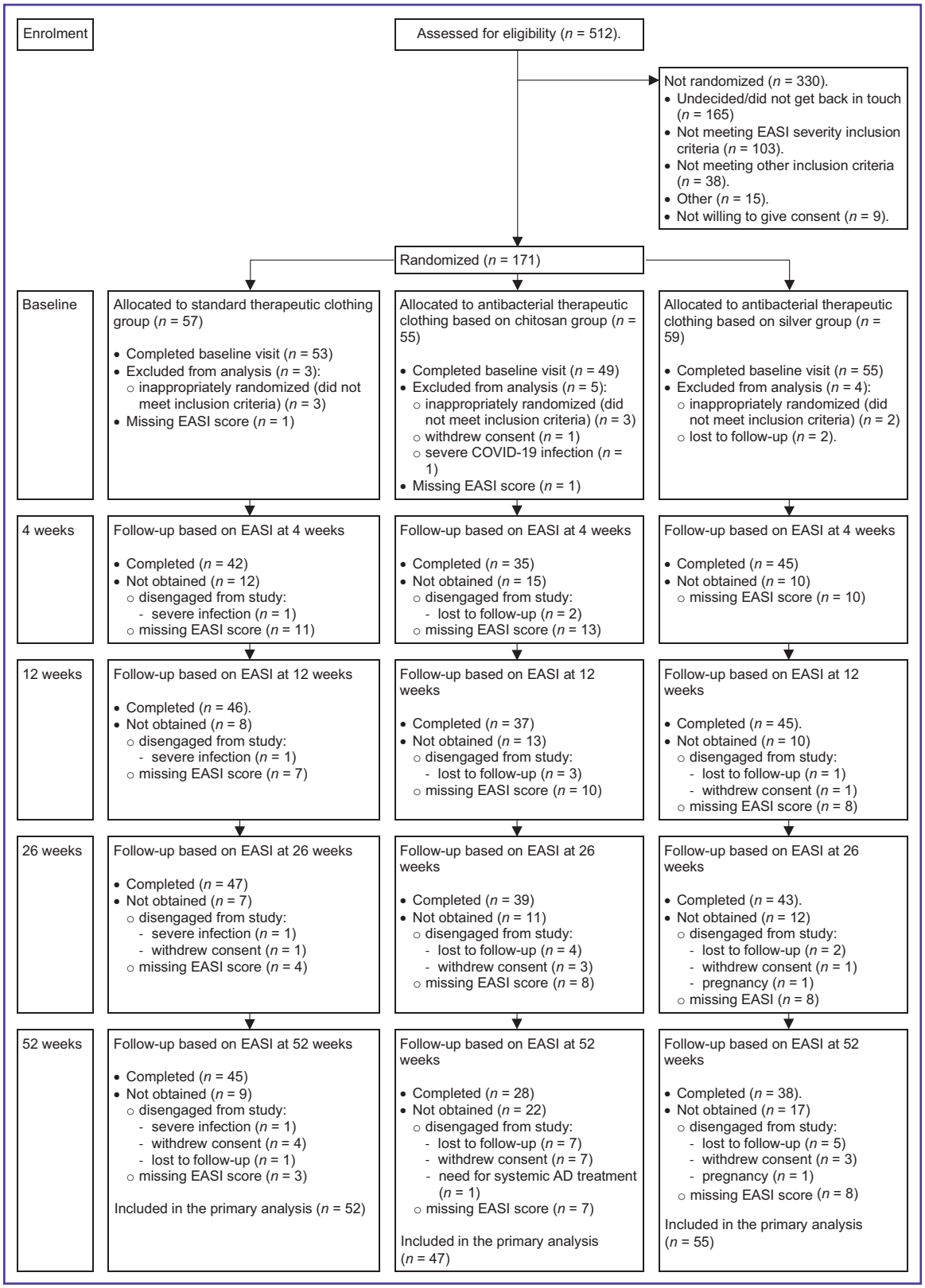

Figure 1 Trial profile: patient flowchart. For each visit the cumulative number of patients that discontinued is presented in addition to the number of missing Eczema Area and Severity Index (EASI) scores at visit.

Table 1 Patient characteristics

Characteristic	Standard therapeutic clothing ($n=54$)	Antibacterial clothing based on chitosan ($n=50$)	Antibacterial clothing based on silver ($n=55$)	Total ($n=159$)
Demographics				
Age (years), median (IQR)	8 (2.8–20.5)	8.5 (4.0–25.0)	8 (3.0–27.0)	8 (3.0–24.0)
Age group (years)				
0–5	22 (41)	21 (42)	21 (38)	64 (40.3)
6–17	17 (31)	14 (28)	17 (31)	48 (30.2)
≥ 18	15 (28)	15 (30)	17 (31)	47 (29.6)
Sex				
Male	21 (39)	21 (42)	31 (56)	73 (45.9)
Female	33 (61)	29 (58)	24 (44)	86 (54.1)
Clinical characteristics (self-reported)				
Fitzpatrick skin type				
I–III	38 (79)	38 (83)	39 (76)	115 (79.3)
IV–VI	10 (21)	8 (17)	12 (24)	30 (20.7)
Age of AD onset (years)				
0–2	44 (86)	38 (83)	46 (85)	128 (84.8)
≥ 3	7 (14)	8 (17)	8 (15)	23 (15.2)
Location of AD				
Head and scalp	34 (63)	35 (70)	32 (58)	101 (63.5)
Hands	20 (37)	22 (44)	17 (31)	59 (37.1)
Feet	12 (22)	10 (20)	8 (15)	30 (18.9)
Limbs	46 (85)	38 (76)	50 (91)	134 (84.3)
Trunk	32 (59)	35 (70)	35 (64)	102 (64.2)
History of atopy				
Asthma	14 (26)	8 (16)	15 (27)	37 (23.3)
Allergic rhinoconjunctivitis	22 (41)	18 (36)	25 (46)	65 (40.9)
Food allergy	23 (43)	19 (38)	20 (36)	62 (39.0)
History of bacterial skin infections				
Impetigo vulgaris	8 (15)	4 (8)	2 (4)	14 (8.8)
Impetiginized AD	9 (17)	4 (8)	16 (29)	29 (18.2)
Other skin infections	4 (7)	9 (18)	3 (5)	16 (10.1)
Previous AD-related therapies				
Antibiotics and antiseptics, including topical	18 (33)	10 (20)	13 (24)	41 (25.8)
Systemic AD treatment, including biologics	8 (15)	7 (14)	7 (13)	22 (13.8)
Phototherapy	8 (15)	4 (8)	8 (15)	20 (12.6)
Therapeutic clothing	19 (35)	11 (22)	10 (18)	40 (25.2)
Current AD care				
GP	5 (11)	10 (22)	5 (10)	20 (14.0)
Paediatrician	2 (4)	0 (0)	5 (10)	7 (4.9)
Dermatologist	33 (73)	32 (70)	37 (71)	102 (71.3)
Self-management	5 (11)	4 (9)	5 (10)	14 (9.8)
Current AD treatment				
Emollients	49 (91)	45 (90)	52 (95)	146 (92)
TCS	45 (83)	38 (76)	44 (80)	127 (80)
TCIs	7 (13)	10 (20)	9 (16)	26 (16)
AD severity				
vIGA-AD				
Clear	0 (0)	0 (0)	0 (0)	0 (0)
Almost clear	0 (0)	2 (4)	0 (0)	2 (1.3)
Mild	10 (20)	9 (18)	12 (22)	31 (20.1)
Moderate	32 (63)	34 (69)	35 (65)	101 (65.6)
Severe	9 (18)	4 (8)	7 (13)	20 (13.0)
IGA for impetiginization				
Absent	40 (78)	38 (81)	40 (75)	118 (78.1)
Mild	9 (18)	6 (13)	13 (25)	28 (18.5)
Extensive	2 (4)	3 (6)	0 (0)	5 (3.3)
EASI, median (IQR)	11.8 (8.9–19.3)	11.3 (7.7–14.1)	11.6 (8.4–16.5)	11.6 (8.4–16.8)
POEM, median (IQR)	16.0 (11.8–21.0)	19.0 (12.5–21.5)	18.0 (10.0–21.0)	17.0 (11.0–21.0)

Data are presented as *n* (%) unless otherwise stated. AD, atopic dermatitis; EASI, Eczema Area and Severity Index; GP, general practitioner; IGA, Investigator Global Assessment; IQR, interquartile range; POEM, Patient Oriented Eczema Measure; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; vIGA, validated Investigator Global Assessment.

intention-to-treat population were generally similar across the intervention groups.

Adherence and therapeutic clothing use

Adherence to all types of therapeutic clothing was high, with patients reporting a median estimated average wearing time of 9 h daily (IQR 8–12) and a median of seven (IQR 3–7) nights per week over the follow-up period (Appendix S10). The comfort of the therapeutic clothing was perceived as (very) good by at least 84% of participants in all groups. Approximately half (57%) of all patients received a second provision of therapeutic clothing and 6% a third provision.

Clinical effectiveness

Investigator-reported outcomes

No difference in AD severity was found [Figure 2, Table 2; Appendix S11 (see Supporting Information)]. The difference in original EASI score over 52 weeks between the standard therapeutic clothing and antibacterial therapeutic clothing based on chitosan was −0.1 [95% confidence interval (CI) −0.3 to 0.2] and −0.1 (95% CI −0.3 to 0.2) in the silver group ($n=154$). However, our model suggested a negligible but significant group × time interaction effect between the nonantibacterial clothing group and antibacterial (based on silver) group, in which patients in the silver group performed slightly worse after 26 weeks of follow-up ($P=0.03$). This implied a difference in the slope at which the EASI decreased over time, with a steeper slope seen in the standard therapeutic clothing group. Similarly, no differences between groups were found in IGA and IGA impetiginization scores [Table 2; Appendix S12 (see Supporting Information)]. However, parallel to EASI, a negligible but significant ($P=0.03$) group × time interaction effect between the standard therapeutic clothing and antibacterial group based on silver was found, in which those in the silver group had higher IGA scores (i.e. worse AD severity) after 26 weeks of follow-up.

Patient-reported outcomes

No overall differences between the standard therapeutic clothing group and antibacterial therapeutic clothing groups were found in POEM, pruritus, sleep disturbance, pain, RECAP, CDLQI, Dermatitis Family Impact, Family DLQI, EQ-5D-5L value, EQ-5D-5L visual analogue scale (VAS), EQ-5D-3L value and EQ-5D-3L VAS scores [Table 3; Appendixes S13–S17 (see Supporting Information)]. However, some differences were found in IDQOL and DLQI scores. Compared with both antibacterial therapeutic clothing groups, adults (aged ≥ 16 years) in the standard therapeutic clothing group had lower DLQI scores [better QoL; $n=36$ (chitosan $P=0.02$; silver $P=0.04$)], while infants (aged 0–3 years) in the standard therapeutic clothing group had higher IDQOI scores (worse QoL) than those in the antibacterial clothing group based on chitosan ($n=31$, $P=0.04$). Based on these findings, post hoc analyses were performed, which showed no age-dependent effect in our primary analysis (Appendix S18; see Supporting Information).

Effect on topical corticosteroid use

No differences in weekly TCS application frequency, TCS potency class and patient-estimated duration of use of a 30-g tube of TCS were found between groups (Appendix S19, S20; see Supporting Information).

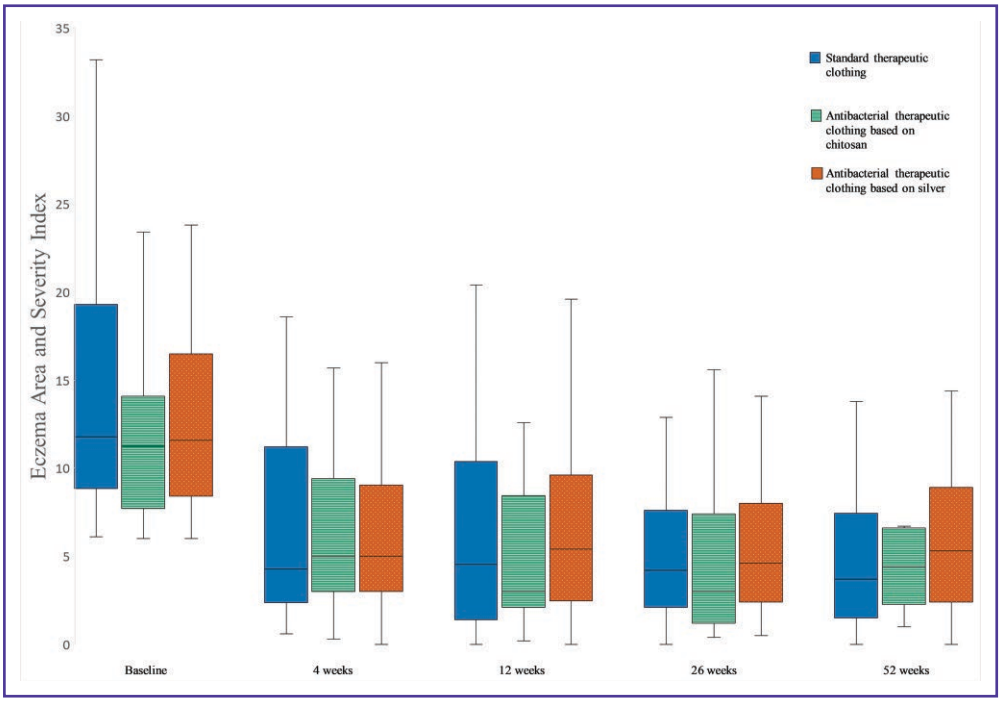

Figure 2 Primary outcome: median atopic dermatitis severity scores (Eczema Area and Severity Index) with interquartile range.

Table 2 Clinical outcomes

Outcome	Allocated group	Timepoint: Baseline	4W (±2W)	12W (±6W)	26W (±8W)	Difference with standard therapeutic over 26W, *P*-value	52W (±12W)	Difference with standard therapeutic over 52W, *P*-value[a]	Time × group interaction over 52W, *P*-value
Outcomes by blinded professionals									
EASI									
	Standard therapeutic clothing								
	n	53	42	46	47	NA	45	NA	NA
	Median (IQR)	11.8 (8.9–19.3)	4.3 (2.4–11.2)	4.6 (1.4–10.4)	4.2 (2.1–7.6)		3.6 (1.5–7.4)		
	Antibacterial therapeutic clothing based on chitosan								
	n	49	35	37	39	0.85	28	0.53	0.10
	Median (IQR)	11.3 (7.7–14.1)	5.0 (3.0–9.4)	3.0 (2.1–8.5)	3.0 (1.2–7.4)		4.4 (2.1–6.6)		
	Antibacterial therapeutic clothing based on silver								
	n	55	45	45	43	0.43	38	0.58	0.03
	Median (IQR)	11.6 (8.4–16.5)	5.0 (3.0–9.1)	5.4 (2.5–9.6)	4.6 (2.4–8.0)		5.8 (2.8–9.0)		
vIGA-AD									
	Standard therapeutic clothing, *n* (%)								
	n	53	43	46	46	NA	44	NA	NA
	Clear/almost clear	0	9 (21)	19 (41)	14 (30)		19 (43)		
	Mild	10 (19)	21 (49)	16 (35)	22 (48)		15 (34)		
	Moderate	32 (60)	8 (19)	7 (15)	9 (20)		9 (20)		
	Severe	9 (17)	4 (9)	4 (9)	1 (2)		1 (2)		
	Antibacterial therapeutic clothing based on chitosan, *n* (%)								
	n	49	36	37	39	0.38	29	0.82	0.06
	Clear/almost clear	2 (4)	9 (25)	14 (38)	16 (41)		6 (21)		
	Mild	9 (18)	16 (44)	11 (30)	12 (31)		15 (52)		
	Moderate	34 (69)	11 (31)	10 (27)	9 (23)		6 (21)		
	Severe	4 (8)	0 (0)	2 (5)	2 (5)		2 (7)		
	Antibacterial therapeutic clothing based on silver, *n* (%)								
	n	54	47	45	42	0.23	37	0.88	0.03
	Clear/almost clear	0 (0)	14 (30)	15 (33)	10 (24)		10 (27)		
	Mild	12 (22)	21 (45)	16 (36)	19 (45)		13 (35)		
	Moderate	35 (65)	8 (17)	12 (27)	12 (29)		11 (30)		
	Severe	7 (13)	4 (9)	2 (4)	1 (2)		3 (8)		
Staphylococcus aureus skin colonization									
	Standard therapeutic clothing								
	n	48	36	46	45	NA	40	NA	NA
	–	13 (27)	23 (64)	29 (63)	29 (64)		24 (60)		
	+	27 (56)	11 (31)	12 (26)	14 (31)		14 (35)		
	++	8 (17)	2 (6)	4 (9)	2 (4)		1 (3)		
	+++ and ++++	0 (0)	0 (0)	1 (2)	0 (0)		1 (3)		
	Antibacterial therapeutic clothing based on chitosan								
	n	46	32	35	32	0.97	26	0.82	0.95
	–	14 (31)	17 (53)	22 (63)	22 (69)		19 (73)		
	+	29 (64)	13 (41)	12 (34)	10 (31)		4 (15)		
	++	2 (4)	2 (6)	1 (3)	0 (0)		2 (8)		
	+++ and ++++	0 (0)	0 (0)	0 (0)	0 (0)		1 (4)		
	Antibacterial therapeutic clothing based on silver								
	n	48	39	43	40	0.89	37	0.93	0.55
	–	18 (39)	25 (64)	23 (53)	27 (68)		20 (54)		
	+	24 (52)	12 (31)	17 (40)	12 (30)		15 (41)		
	++	3 (7)	2 (5)	2 (5)	1 (3)		1 (3)		
	+++ and ++++	1 (2)	0 (0)	1 (2)	0 (0)		1 (3)		

EASI, Eczema Area and Severity Index; IQR, interquartile range; NA, not applicable; vIGA-AD, validated Investigator Global Assessment for atopic dermatitis; W, weeks. [a]Primary outcome.

Table 3 Patient-reported outcomes

Outcome	Allocated group		Timepoint							
			Baseline	4W	12W	26W	Difference with standard therapeutic over 26W, *P*-value	52W	Difference with standard therapeutic over 52W, *P*-value (Primary outcome)	Time × group interaction over 52W, *P*-value
POEM										
	Standard therapeutic clothing									
	n		46	46	40	39	NA	39	NA	NA
	Median (IQR)		15.0 (10.8–18.0)	9.0 (4.0–14.0)	6.0 (3.0–11.8)	8.0 (5.0–12.0)		6.0 (3.0–10.0)		
	Antibacterial therapeutic clothing based on chitosan									
	n		44	34	37	36	0.11	34	0.64	0.05
	Median (IQR)		16.0 (12.3–19.0)	10.5 (5.0–16.0)	11.0 (4.5–15.0)	10.5 (7.0–13.0)		11.0 (5.0–15.0)		
	Antibacterial therapeutic clothing based on silver									
	n		52	44	40	35	0.99	40	0.75	0.55
	Median (IQR)		13.5 (9.3–17.8)	9.0 (4.3–12.0)	7.5 (4.3–12.0)	6.0 (4.0–9.0)		8.5 (5.0–13.0)		
NRS for peak pruritus										
	Standard therapeutic clothing									
	n		43	46	38	41	NA	38	NA	NA
	Median (IQR)		7.0 (5.0–8.0)	4.0 (1.5–7.0)	5.8 (1.0–5.1)	4.0 (1.8–7.0)		3.0 (1.0–7.0)		
	Antibacterial therapeutic clothing based on chitosan									
	n		43	33	36	34	0.13	33	0.12	0.93
	Median (IQR)		7.0 (5.0–8.0)	5.0 (2.3–6.5)	5.0 (3.0–6.9)	5.1 (3.0–7.0)		7.0 (2.0–8.0)		
	Antibacterial therapeutic clothing based on silver									
	n		47	41	38	32	0.98	37	0.50	0.41
	Median (IQR)		6.5 (3.0–8.0)	4.0 (1.0–6.0)	2.0 (1.0–6.0)	2.8 (1.0–4.9)		3.0 (2.0–6.0)		
RECAP										
	Standard therapeutic clothing									
	n		44	46	38	39	NA	37	NA	NA
	Median (IQR)		15.0 (10.0–18.0)	9.0 (4.0–14.0)	6.0 (3.0–11.3)	8.0 (5.0–12.0)		6.0 (3.0–10.0)		
	Antibacterial therapeutic clothing based on chitosan									
	n		43	33	36	35	0.09	32	0.36	0.27
	Median (IQR)		16.0 (11.5–19.3)	10.0 (5.0–15.5)	10.5 (4.3–15.0)	10.0 (7.0–13.0)		11.0 (5.0–15.0)		
	Antibacterial therapeutic clothing based on silver									
	n		50	42	38	33	0.51	37	0.88	0.12
	Median (IQR)		13.5 (8.8–18.0)	9.0 (3.8–12.0)	7.5 (4.0–12.3)	6.0 (4.0–9.0)		8.0 (5.0–13.0)		
DLQI										
	Standard therapeutic clothing									
	DLQI	*n*	8	11	11	14	NA	13	NA	NA
		Median (IQR)	11.0 (3.5–11.0)	3.0 (2.0–5.0)	3.0 (1.0–8.0)	2.0 (1.8–4.5)		3.0 (1.0–3.5)		
	CDLQI	*n*	19	17	17	13	NA	14	NA	NA
		Median (IQR)	9.0 (4.0–11.0)	5.0 (2.5–9.5)	5.0 (2.5–8.5)	5.0 (3.5–7.5)		5.5 (2.0–7.3)		
	IDQOL	*n*	15	15	11	11	NA	9	NA	NA
		Median (IQR)	13.0 (7.0–15.0)	10.0 (5.0–12.0)	7.0 (2.0–12.0)	6.0 (3.0–11.0)		2.0 (0.5–3.0)		

(*Continued*)

Table 3 (*Continued*)

			Timepoint							
Outcome	**Allocated group**		**Baseline**	**4W**	**12W**	**26W**	**Difference with standard therapeutic over 26W, *P*-value**	**52W**	**Difference with standard therapeutic over 52W, *P*-value (Primary outcome)**	**Time × group interaction over 52W, *P*-value**
	Antibacterial therapeutic clothing based on chitosan									
	DLQI	*n*	13	10	12	13	0.05	11	0.02	0.64
		Median (IQR)	13.0 (9.5–17.0)	9.5 (3.8–13.0)	8.5 (5.0–13.0)	8.0 (4.0–10.0)		7.0 (4.0–12.0)		
	CDLQI	*n*	19	13	16	18	0.40	16	0.76	0.17
		Median (IQR)	9.0 (5.0–11.0)	7.0 (4.0–9.5)	8.5 (4.5–10.0)	7.0 (5.0–10.5)		8.5 (5.0–12.0)		
	IDQOL	*n*	8	7	7	4	0.85	4	0.04	0.04
		Median (IQR)	11.5 (8.0–16.5)	5.0 (2.0–8.0)	4.0 (3.0–4.0)	2.5 (1.3–3.8)		5.0 (3.3–13.5)		
	Antibacterial therapeutic clothing based on silver									
	DLQI	*n*	18	12	15	13	0.03	14	0.04	0.89
		Median (IQR)	8.0 (6.8–13.0)	9.5 (6.5–12.8)	4.0 (3.0–11.0)	4.0 (1.0–7.5)		4.0 (2.0–11.0)		
	CDLQI	*n*	17	18	11	11	0.66	13	0.24	0.50
		Median (IQR)	9.0 (5.5–12.5)	7.0 (3.0–8.5)	5.0 (2.0–6.0)	4.0 (2.0–7.0)		5.0 (3.5–7.5)		
	IDQOL	*n*	13	11	10	8	0.97	13	0.26	0.17
		Median (IQR)	5.0 (4.0–6.5)	4.0 (3.0–6.0)	4.0 (1.8–5.0)	4.0 (2.3–5.0)		3.0 (1.5–5.0)		

CDLQI, Children's Dermatology Life Quality Index; DLQI, Dermatological Life Quality Index; IDQOL, Infants' Dermatitis Quality of Life Index; IQR, interquartile range; NA, not applicable; NRS, numerical rating scale; RECAP, Recap of atopic dermatitis; POEM, Patient Oriented Eczema Measure; W, weeks.

Effect on *Staphylococcus aureus* colonization

With regard to SA colonization, no differences between the standard and antibacterial therapeutic clothing groups were found (Table 2).

Safety outcomes and silver absorption

No differences in (skin-related) AEs (e.g. number of skin infections) were found between groups (Appendix S21; see Supporting Information). Furthermore, possible signs of silver deposition, such as argyria, were not detected throughout the study. After 1 year of continuous use of therapeutic clothing based on silver, a urine silver concentration of 0.4 $\mu g\ L^{-1}$ (reference value 1 $\mu g\ L^{-1}$) was detected in one patient (Appendix S22; see Supporting Information). No silver was detected in any other patient.

Healthcare utilization

No differences in registered healthcare utilization (e.g. dermatological consultations) and cost of therapeutic clothing prescriptions between groups were found (Appendix S23, S24; see Supporting Information). Furthermore, no differences in self-reported healthcare utilization and out-of-pocket costs were found between groups (Appendix S25, S26; see Supporting Information).

Discussion

In this 1-year pragmatic study, the effectiveness of nonantibacterial therapeutic clothing in addition to basic topical treatment was compared with that of antibacterial clothing based on silver and chitosan in patients with moderate-to-severe AD. No differences were found between groups in AD severity, patient-reported symptoms, QoL, TCS use, SA skin colonization, safety and healthcare utilization. The results of this study suggest no additional benefits of antibacterial agents in therapeutic clothing in patients with moderate-to-severe AD, when therapeutic clothing is used in addition to topical treatment.

Contrary to previous (pilot) studies, but similarly to the CLOTHES trial of Thomas *et al.*, we did not find support for the added benefit of antibacterial agents.[26–39] Several factors may explain this discrepancy. Firstly, compared with our study, all other studies had small sample sizes ($n = 12–68$), which could yield false-positive outcomes and publication bias may have contributed to absence of studies with negative outcomes.[40,41] Next, most previous studies restricted TCS use to investigate the efficacy of antibacterial therapeutic clothing, but this limits their generalizability to real-world settings in which patients use therapeutic clothing as an addition to (topical) treatment. Thirdly, the absence of blinding and the involvement of manufacturers of therapeutic clothing in some studies may have influenced the results. Finally, many studies had a short follow-up duration (7–28 days), which restricts insights into effectiveness over time and disease course.

In contrast to previous studies, both our study and the CLOTHES trial incorporated a pragmatic approach, comprehensive outcome measures and long-term follow-up. Additionally, both studies investigated in a way that closely resembled real-life use of therapeutic clothing in AD, increasing the generalizability of their findings. While some have questioned the inclusion of patients with mild AD in the CLOTHES trial (median baseline EASI of ±7), as they claim therapeutic clothing is generally prescribed to patients with moderate-to-severe AD, we only included patients with moderate-to-severe AD (median baseline EASI of ±11.6), based on the severity strata proposed by Chopra *et al.*,[14] and found similar results. Although our study was confronted with missing data, mainly due to the COVID-19 pandemic, our primary analysis included sufficient data to address our main objective. Furthermore, the consistency observed among the outcome measures supports our belief that antibacterial therapeutic clothing is not superior to standard nonantibacterial therapeutic clothing. Selection, detection, performance and attrition biases are unlikely to account for the lack of effectiveness of antibacterial therapeutic clothing. AD signs and symptoms were measured with a comprehensive set of validated outcome measures by both blinded patients and professionals.

The therapeutic clothing used in this trial is commonly used in the Netherlands and frequently prescribed by professionals. Although minor differences in shape, fit and materials between Binamed (BAP Medical; standard and antibacterial clothing based on silver) and DermaCura (D&M; antibacterial clothing based on chitosan) exist – which could restrict a 'clean analysis' between these groups – we believe that the addition of the chitosan group provides a wider understanding of the role of antibacterial therapeutic clothing in AD. However, as both types of antibacterial therapeutic clothing were unable to reduce SA colonization more than standard therapeutic clothing, we cannot exclude that other therapeutic clothing with a greater antibacterial effect may be effective. It should be noted that SA colonization was low in all groups at the end of the study and the inflammatory properties of SA are believed to be quantity dependent.[42]

Our finding that antibacterial therapeutic clothing is not superior to standard therapeutic clothing is in line with a Cochrane review that showed no relevant benefit from antistaphylococcal interventions in AD.[43] Although the antibacterial properties of chitosan and silver have been demonstrated previously, our results showed no additional reduction in skin SA colonization in these intervention groups.[7,27] Several factors may contribute to this finding. Among other factors, adequate basic treatment with TCS and emollients provided during the follow-up period may have reduced SA colonization sufficiently to suppress the inflammatory properties of SA.[44] Next, the antibacterial properties of therapeutic clothing may be insufficient to reduce SA colonization under real-world conditions, as demonstrated in a study that showed that the antibacterial effect of silver filaments depends on unrealistically moist conditions.[45] Furthermore, a 2022 study suggested that reducing SA colonization and restoring cutaneous dysbiosis in moderate AD may not be a successful treatment strategy to reduce clinical symptoms.[46] In this study, an antimicrobial peptide showed strong effects on SA reduction, but no clear signal in markers believed to be involved in AD inflammation. However, as certain AD subpopulations may be more susceptible to SA colonization, such as patients with filaggrin loss-of-function mutations, it could be speculated that

some subpopulations may benefit (more) from antibacterial therapy.[47] As the inflammation-inducing properties of SA have been well documented, antibacterial treatment may still be interesting in AD.[48] Future studies should focus on identifying these patient subpopulations and evaluate the effectiveness of antibacterial interventions in them.

Based on our results, we assumed that therapeutic clothing, including clothing based on silver, is generally safe. Although silver was detected in one patient at the end of follow-up, the urinary silver concentration was far below the normal value. Furthermore, at this concentration, the positive result could easily have been caused by contamination.[49] In line with previous studies, we assume no relevant transcutaneous silver adsorption from silver-containing therapeutic clothing in AD.[37,50]

This pragmatic study aimed to evaluate the effectiveness of antibacterial therapeutic clothing in a real-world setting. The effectiveness was evaluated on all important domains, ranging from objective AD severity to TCS use, offering a comprehensive and conclusive overview. Furthermore, the pragmatic nature of this trial and good adherence throughout the follow-up period increases its external validity, making the findings more applicable to real-world settings. A limitation to this study may be the minor differences in composition and fit of therapeutic clothing, which may have limited a 'clean' analysis of the effectiveness of added chitosan. Furthermore, patients who previously used (antibacterial) therapeutic clothing may have noticed these differences, which could have led to blinding issues. However, as no difference in the supposed mechanism of action (reduction of SA colonization) was found, it is unlikely that these differences would have altered the outcome. A limitation of our study was the number of patients lost to follow-up and missing data. While the COVID-19 pandemic may have contributed to this, other factors, such as satisfactory response to overall treatment or a (perceived) lack of effect, might also have played a role. Additionally, this study was powered to detect a clinically meaningful difference, which represents a medium effect in this study. Despite these limitations, the results indicated no clinically relevant superiority of antibacterial over standard therapeutic clothing. Finally, as the outcomes in all groups improved, it is possible that the added effectiveness of antibacterial agents was masked by general trial effects.

In this pragmatic study, no evidence was found to support the superiority of antibacterial therapeutic clothing in terms of alleviating AD signs and patient-reported symptoms, improving QoL, reducing TCS use, suppressing SA skin colonization, reducing AEs or lowering healthcare utilization. The findings suggest that antibacterial agents in therapeutic clothing are unlikely to provide additional benefits for patients with AD. Future research should aim to identify specific AD subpopulations that may exhibit increased susceptibility to SA and assess the impact of antibacterial interventions in these groups.

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Conflicts of interest

The Department of Dermatology of the Erasmus MC University Medical Centre Rotterdam received an unrestricted grant from BAP Medical, D&M and DeclaCare (part of BENU Netherlands). S.G.M.A.P. is an advisor, consultant, speaker and/or investigator for LEO Pharma, Regeneron Pharmaceuticals, Sanofi Genzyme, Novartis and Pierre Fabre; and has received grants from Novartis and Pierre Fabre, BAP Medical, D&M and DeclaCare (part of BENU Netherlands). M.L.A.S. is an advisor, consultant, speaker and/or investigator for AbbVie, Pfizer, LEO Pharma, Regeneron, Sanofi Genzyme, Eli Lilly and Galderma; and has received grants from Regeneron, Sanofi Genzyme, Novartis and Pfizer. M.d.G. is a consultant, advisory board member and/or speaker for AbbVie, Almirall, Eli Lilly, Janssen, LEO Pharma, Novartis, Pfizer, Regeneron Pharmaceuticals and Sanofi. R.A.T. has attended advisory boards from LEO Pharma, UCB Pharma, Novartis Pharma and Eli Lilly Netherlands. T.R. is an advisor, speaker and/or investigator for LEO Pharma, Sanofi Genzyme, Novartis, Pfizer, SmartPractice and BAP Medical.

Data availability

The data that support the findings of this study are available upon request from the corresponding author. The data are not publicly available owing to privacy restrictions.

Ethics statement

The antibacterial clothing study protocol was approved by the Medical Ethics Committee of the Erasmus MC University Medical Centre Rotterdam, the Netherlands (reference 2018-1609). Written informed consent was provided by all participants and parents/guardians. This study was conducted in compliance with the Declaration of Helsinki and all International Conference on Harmonization Good Clinical Practice guidelines.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

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