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REVIEW

Intestinal carriage of *Staphylococcus aureus*: how does its frequency compare with that of nasal carriage and what is its clinical impact?

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Abstract The bacterial species *Staphylococcus aureus*, including its methicillin-resistant variant (MRSA), finds its primary ecological niche in the human nose, but is also able to colonize the intestines and the perineal region. Intestinal carriage has not been widely investigated despite its potential clinical impact. This review summarizes literature on the topic and sketches the current state of affairs from a microbiological and infectious diseases' perspective. Major findings are that the average reported detection rate of intestinal carriage in healthy individuals and patients is 20% for *S. aureus* and 9% for MRSA, which is approximately half of that for nasal carriage. Nasal carriage seems to predispose to intestinal carriage, but sole intestinal carriage occurs relatively frequently and is observed in 1 out of 3 intestinal carriers, which provides a rationale to include intestinal screening for surveillance or in outbreak settings. Colonization of the intestinal tract with *S. aureus* at a young age occurs at a high frequency and may affect the host's immune system. The frequency of intestinal carriage is generally underestimated and may significantly contribute to bacterial dissemination and subsequent risk of infections. Whether intestinal rather than nasal *S. aureus* carriage is a primary predictor for infections is still ill-defined.

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Introduction

Nasal colonization by *Staphylococcus aureus* is a well-established risk factor for acute cutaneous infections, post-operative infections, as well as most other types of *S. aureus* infections [1–3]. Several recent studies have suggested that lasting colonization of *S. aureus* in the human intestinal tract also occurs and that this may have important clinical implications. Still, compared to nasal carriage, gastro-intestinal colonization by *S. aureus* has been sparsely studied.

In the 1950s and 1960s, intestinal *S. aureus* carriage was first defined and studied as a potential cause of antibiotic-associated diarrhea (AAD) [4]. However, after the identification of *Clostridium difficile* as the most common pathogen of hospital-acquired AAD in the 1970s [5], the role of gastro-intestinal colonization as a risk factor for (intestinal) *S. aureus* infection has been neglected for decades and the issue has only recently re-emerged. The pandemic rise in the incidence of methicillin-resistant *S. aureus* (MRSA) strains, as opposed to methicillin-sensitive *S. aureus* (MSSA), has contributed greatly to the renewed interest in intestinal *S. aureus* colonization. This covered investigations into risk factors for both AAD as well as health care-associated (HA) infections. Furthermore, community-acquired (CA) MRSA infection among individuals without "HA risk factors" was first recognized in the late 1990s. CA-MRSA is now emerging as an apparent epidemic. In recent studies, in addition to nasal carriage, rectal carriage of CA-MRSA has also been documented. In this review we will give an historical update and a systemic overview of the more recent studies related to intestinal and/or perineal carriage of *S. aureus* (MSSA, HA-MRSA, and CA-MRSA) and we will discuss its clinical implications.

Culture methods and definition of perineal and intestinal carriage

Techniques to determine carriage or colonization can be based on classical culture assays using selective broths or agars for MSSA, as well as novel growth-based phenotypic and molecular methods for both MSSA and MRSA detection [6]. Methods used to define intestinal carriage include culture of stool, rectal swabs or anal swabs. Also, swabs from the perianal area (including the perineum and the groin or inguinal region) are generally accepted to define intestinal carriage. For these sites, however, it can be argued that these may also represent skin carriage. In a limited number of reports direct comparison of the frequency yields for these different sites of colonization within the same study have been presented. Rectal swabs were reported to have higher yields of *S. aureus* detection than stool cultures [7], but a more recent comparison [8] gave opposite results for MRSA. Other studies reported similar frequencies of carriage for both perianal and groin sites of carriage for nursing home residents and hospitalized patients respectively [9, 10]. Also, direct comparisons of the rectal and perineal sites gave similar frequencies of detection [11] and in another recent study screening of the perineal area, the rectum and the inguinal area gave similar frequencies of detection of MRSA [12], which legitimates the use of all of these sites to define intestinal carriage.

Intestinal carriage frequencies of *S. aureus* in adults

Most early studies on the intestinal carriage of *S. aureus* were performed on hospitalized patients and timely overviews of frequencies of intestinal carriage in adults upon admission to the hospital were reported [4, 13]. The frequencies found in these relatively ancient studies ranged from 8 to 31% (Table 1). Among adults, nasal *S. aureus* carriers were reported to yield *S. aureus* from their feces more often than non-nasal carriers did. Strain typing suggested involvement of the same strains for both colonization sites [14]. Vice versa, about 50–70% of perineal carriers were also nasal carriers of the same strain [15]. It was reported that of 50 healthy male students screened, 11 (22%) had perineal carriage of *S. aureus* and that 5 of these were non-nasal carriers (10%) [16]. This implied that non-nasal carriers might be susceptible to intestinal carriage, suggesting that mechanisms for nasal and intestinal carriage differ.

More recent data on the intestinal carriage of *S. aureus* in adults were generated as part of studies mostly aimed at identifying MRSA. In most of these studies the patients were screened for intestinal as well as nasal carriage, allowing a comparison of these sites of colonization

Table 1 Reported frequencies of intestinal carriage of *S. aureus* in adults upon admission to hospital in early studies

Reference	Percentage positives
[92]	18
[93]	17
[14]	23
[94]	31
[95]	8
[16]	22
[96]	21
[15]	12
[97]	13

(Table 2). For instance, in a study on 500 pregnant women attending an antenatal clinic a frequency of intestinal carriage of *S. aureus* of 12% (59 patients) and a nasal carriage frequency of 24% (120 patients) were reported [17]. Interestingly, 8% (41) of the patients had intestinal carriage in the absence of nasal carriage, covering 25% of all *S. aureus*-positive patients. Among patients in a skilled nursing facility, nasal and rectal swabs or stools were surveyed for MSSA and MRSA. Of these, 22% (76 patients) had intestinal carriage of *S. aureus* [18]. Ten percent of the patients (n=34) were intestinal carriers in the absence of nasal carriage.

The prevalence of *S. aureus* colonization of the perineum was examined in a longitudinal study on 84 community-dwelling adults with spinal cord dysfunction [19]. *S. aureus* was detected in 20 (24%) individuals. Nasal carriage was detected in 55% of all patients from a subset of 22 patients of whom 23% had intestinal carriage only. By follow-up of 30 patients with at least five cultures for 1 year, the perineal carriage pattern was assessed. They found that 10% had persistent carriage, 63% had intermittent carriage, and 27% were non-carriers, in agreement with nasal carriage patterns [1]. Paired perineal/nasal carriage was determined for 22 participants. Of the 16 perineal carriers in this group, 5 did not have nasal carriage. Among the 11 with both perineal and nasal carriage, all but 1 carried the same *spa* type at both sites. Many similar studies were performed, the results of which are summarized in Table 2.

Altogether the frequency of nasal carriage detection of *S. aureus* ranged from 24% to 61% and intestinal carriage frequencies in these studies ranged from 10% to 37%. These ranges probably reflect the different criteria used for the selection of patient groups and the differences in risk of *S. aureus* colonization or infection amongst these heterogeneous groups of patients from different geographical regions. Therefore, calculation of an overall frequency of *S. aureus* carriage from these studies by using actual total numbers of patients may be debated, but, nevertheless, results in approximately 20% of cases of intestinal carriage

Table 2 Frequencies of detection of *S. aureus* (including MRSA) with regard to intestinal and nasal carriage and intestinal carriage in the absence of nasal carriage in adults

Reference	Total number of patients screened	Intestinal carriage, percentage of total (*n*) or (*n*/total)	Nasal carriage, percentage of total (*n*) or (*n*/total[a])	Intestinal carriage in the absence of nasal carriage, percentage of total (*n*/total[a])	Intestinal carriage in the absence of nasal carriage, percentage of intestinal carriers (*n*/total[a])	Method used	Patient group
[17]	500	12 (59)	24 (120)	8 (41)	70	Perineal swabs	Pregnant women
[77]	37	24 (9)	30 (15/50)	NS	NS	Rectal swab	Mothers 1 week after delivery
[55]	62	11 (7)	44 (27)	3 (2)	29	Perineal swabs	Healthy adults
[18]	354	22 (76)	61 (214)	10 (34)	45	Stools	Private SNF patients
[48]	204	29 (59)	47 (96)	3 (7)	12	Rectal swabs	ICU liver transplant patients
[24]	231	10 (24)	30 (70)	5 (11)	46	Perineal swabs	Intensive care patients
[90]	94	37 (35)	49 (47/96)	10 (9)	26	Rectal swabs	Liver transplant recipients
[44]	71	37 (26)	51 (36)	4 (3)	12	Stools	Selected inpatients
[10]	213	25 (54)	43 (91)	NS	NS	Perianal swabs	Nursing home residents
Totals	1,766	20 (349/1,766)	40 (716/1,781)	8 (112/1,538)	37 (112/302)		

NS, not specified; SNF, skilled nursing facilities; ICU, intensive care unit
[a] Totals are indicated when frequencies are based on a different total number of patients screened

compared with nasal carriage of approximately 40%. When reported frequencies of the separate studies are plotted, it appears as if there is a linear correlation between the incidence of nasal and intestinal carriage (see Fig. 1). The slope of the linear regression is 0.55, which suggests that intestinal carriage is probably preceded by nasal carriage. However, sole intestinal carriage also seems to occur with frequencies ranging from 3–10%. When intestinal carriage in the absence of nasal carriage is calculated from these studies using actual numbers of patients a figure of 8% is obtained. Furthermore, on average, 1 out of 3 intestinal carriers (37%) does not seem to be colonized in the nares (Table 2).

Obviously, compared with nasal carriage the intestinal carriage of *S. aureus* is less frequent, but still may have important clinical consequences.

Intestinal MRSA in adult patients at high risk

During the last 2 decades, a number of studies have reported intestinal screening to determine carriage of MRSA beyond the nasal cavity, in patients at high risk of MRSA at admission or during a stay in a hospital (Table 3). Long-term care patients were analyzed and detection of MRSA was reported in stools from 29 out of 354 patients (8%) [18]. Nasal carriage frequency was 15% (52 patients). The detection of 2 MRSA patients on the basis of 10 stool cultures (20%), obtained during an outbreak in an institution for adults with developmental disabilities, was reported, whereas nasal screening detected MRSA in 16 out of 28 patients (57%) [20]. A frequency of intestinal carriage of 10% (8 out of 84) in community-dwelling patients with spinal cord dysfunction was recorded [19]. Nasal screening of a subgroup of 22 of these patients revealed a nasal MRSA frequency of 55% (12 patients). Furthermore, 205 patients were analyzed who were known to be previously colonized and/or infected with MRSA. Intestinal carriage detection frequency was 33% and nasal carriage detection frequency was 52% [21]. Many other reports describing similar data are surveyed in Table 3. When totals are calculated from these reports, the average nasal carriage frequency in these patients at high risk was 12% and intestinal carriage frequency was 9%.

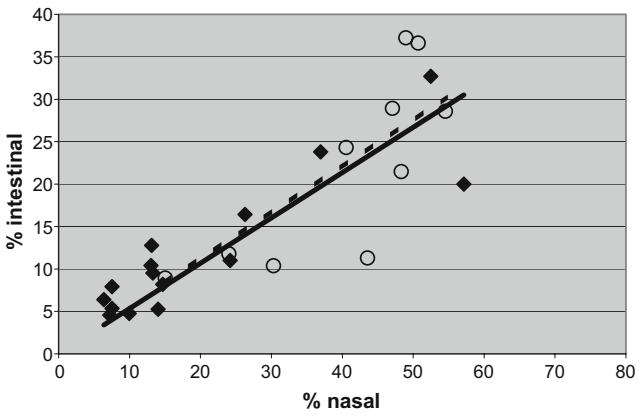

Fig. 1 Relation between frequencies of nasal and intestinal carriage for *S. aureus* (*circles*) and for MRSA (*diamonds*). Lines show the linear regression of *S. aureus* (*dotted line*) and MRSA (*straight line*), the slope of the linear regression lines are 0.55 and 0.53, and R^2 are 0.6012 and 0.7381 for *S. aureus* and MRSA respectively. The plotted data for *S. aureus* are extracted from: [3, 10, 17–19, 24, 44, 48, 77, 90] and for MRSA from: [10, 18–21, 23, 24, 27, 31, 33, 36, 38, 39, 51, 91]

Table 3 The MRSA intestinal carriage and nasal carriage detection frequencies in hospitalized adult patients at high risk

Reference	Total patients screened	Intestinal MRSA, percentage of total (*n*)	Nasal MRSA percentage of total (*n*/total[a])	Method used
[18]	354	8 (29)	15 (52)	Stools
[38]	114	5 (6)	14 (16)	Rectal swabs
[51]	327	11 (36)	24 (117/484)	Stools
[20]	10	20 (2)	57 (16/28)	Perineal swabs
[33]	411	5 (22)	7 (31)	Perineal swabs
[91]	105	10 (10)	13 (34/256)	Perineal swabs
[24]	231	5 (11)	10 (23)	Perineal swabs
[27]	1,250	5 (57)	7 (90)	Rectal swabs
[23]	192	10 (20)	13 (25)	Groin swabs
[31]	1,181	13 (151)	13 (155)	Groin swabs
[39]	845	6 (54)	6 (54)	Rectal swabs
[19]	84	24 (20)	37 (17/46)	Perineal swabs
[21]	52	33 (17)	52 (53/101)	Groin swabs
[36]	758	8 (60)	8 (57)	Perineal swabs
[10]	213	16 (35)	26 (56)	Perineal swabs
Totals	6,127	9 (530/6,127)	12 (796/6,464)	

[a] Totals are indicated when frequencies are based on different numbers of total patients screened.

Interestingly, when frequencies of nasal and intestinal MRSA carriage are plotted and compared with those reported for *S. aureus* (Fig. 1) it seems that the incidence of carriage of MRSA is lower than that for *S. aureus* for both the nares and the intestines, which makes sense, since MRSA has been emerging and disseminating as a colonizing bacterium much more recently than *S. aureus* has. However, the slope of the regression of 0.53 for MRSA is the same as that determined for *S. aureus* (0.55), which indicates a similar relation between both sites of carriage for MRSA and suggests that antibiotic resistance does not influence the relative colonization ability for these two sites.

Distribution of MRSA detection sites

Direct comparison of the distribution of intestinal carriers versus nasal carriers amongst MRSA-colonized patient groups could be deduced from 22 reports (Table 4) [9, 10, 13, 18, 19, 22–29, 31–39]. Table 4 surveys the frequency of patients with intestinal carriage and nasal carriage expressed as a percentage of all MRSA-colonized patients found in the various studies. In general, patients were considered colonized when at least two consecutive cultures from any place in the body grew MRSA, but also single colonization criteria were applied. The frequencies reported ranged from 5 to 76% and from 34 to 84% for intestinal and nasal carriage respectively. When the distribution of intestinal and nasal carriage in MRSA-colonized patients is calculated from all of these studies comprising more than 2,000 MRSA-colonized/infected patients, an overall contribution of 45% is found for intestinal carriage and 58% for nasal carriage for all MRSA-colonized patients.

In Table 4 the reported frequencies of intestinal MRSA carriage in the absence of nasal carriage are also summarized. For instance, in a study of an MRSA outbreak involving a total of 975 MRSA patients, perineal screening identified an additional 15% of culture-positive individuals compared with nasal screening only [25]. In this study, the intestines were reported to be the only positive site out of five culture sites in 10% of the cases. Klotz and coworkers reported that in addition to a high frequency of 24% MRSA-positive stool cultures, 13% of the MRSA strains were first observed in the stool before detecting MRSA in other material from these patients [30]. Similarly, in a large Canadian surveillance study [40], comprising more than 10,000 adult patients, the perineal area was found to be the initial site of MRSA colonization or infection in 41% of the cases. In patients older than 65 years of age, the perineum or rectum was the only positive site in 13%, indicating that nasal screening alone would be sub-optimal in elderly patients. More recently, Zhang et al. [39] reported that nasal screening alone would have detected 76% of MRSA carriers and that the inclusion of rectal screening increased the detection sensitivity to 96%, indicating 20% rectal carriers without nasal carriage. Reyes et al. [36] reported an intestinal carriage frequency without nasal carriage in 27% of their MRSA-positive patients, whereas Mody et al. [10] showed that 23% of their MRSA carriers were only colonized in the perianal area. Altogether, comparisons of rates of nasal and intestinal carriage of MRSA were recorded in 16 of the studies mentioned (Table 4). It can be calculated from these studies that of all MRSA colonized patients, 58% were colonized in the nares, whereas 45% were colonized in the intestines. Of the individuals with gastro-intestinal MRSA, 1 out of 3 (35%) did not carry

Table 4 Distribution of intestinal and nasal carriage in all MRSA-colonized patients detected in the studies

References	Total MRSA cases	Intestinal MRSA, percentage of total (*n*)	Nasal MRSA, percentage of total (*n*/total[a])	Intestinal without nasal, percentage of total (*n*)	Intestinal without nasal, percentage of intestinal carriers	Method used	Patient group
[22]	63	5 (3)	34 (24/79)	Not specified	Not specified	Perineal swabs	General hospital patients, MRSA outbreak
[13]	117	61 (70)	53 (62)	Not specified	Not specified	Rectal swabs	General hospital patients, MRSA outbreak
[26]	11	18 (2)	55 (6)	0 (0)	0	Anal swabs	SCI patients
[32]	67	25 (17)	58 (37)	Not specified	Not specified	Perineal swabs	SCI patients
[25]	723	40 (289)	47 (369/789)	15 (145)	50	Perineal swabs	Hospital MRSA outbreak
[18]	62	47 (29)	84 (52)	16 (10)	35	Stools	Private skilled nursing facility patients
[35]	23	17 (4)	65 (15)	9 (2)	50	Perineal swabs	Acute care patients
[34]	19	42 (8)	68 (13)	5 (1)	13	Perineal swabs	Acute rehabilitation unit SCI patients
[38]	24	25 (6)	67 (16)	8 (2)	33	Rectal swabs	Skilled care unit patients
[33]	51	54 (22)	61 (31)	18 (9)	41	Perianal swabs	Acute rehabilitation unit
[37]	36	50 (18)	75 (27)	25 (9)	50	Groin swabs	General hospital, at risk patients
[28]	203	26 (52)	44 (89)	Not specified	Not specified	Perineal swabs	Neurosurgery unit patients
[29]	35	20 (7)	75 (21)	Not specified	Not specified	Perineal swabs	General hospital, at risk patients
[24]	30	37 (11)	77 (23)	17 (5)	46	Perineal swabs	ICU patients
[9]	96	49 (47)	72 (72)	Not specified	Not specified	Perineal swabs	University hospital, at risk patients
[27]	123	46 (57)	73 (90)	19 (23)	40	Rectal swabs	ICU patients
[23]	31	65 (20)	80 (25)	19 (6)	30	Groin swabs	General hospital, at risk patients
[31]	224	67 (151)	69 (155)	12 (26)	17	Groin swabs	ICU patients
[39]	71	76 (54)	76 (54)	20 (14)	26	Rectal swabs	General hospital, at risk patients
[19]	22	73 (16)	71 (12/17)	30 (5)	31	Perineal swabs	Community-dwelling SCD patients
[36]	78	77 (60)	73 (57)	27 (21)	35	Perineal swabs	ICU patients and other risk factors
[10]	86	41 (35)	65 (56)	11 (9)	11	Perianal swabs	Nursing home residents
Totals	2,195	45 (978/2,195)	58 (1,306/2,268)	18 (287/1,614)	35 (287/833)		

SCI, spinal cord injury; SCD, spinal cord dysfunction

[a] Totals are indicated when frequencies reported are based on different total numbers of cases

MRSA in the nose. Of all MRSA-colonized individuals detected in these studies more than 1 out of 6 (18%) presented with intestinal carriage in the absence of nasal carriage. Such frequencies suggest that the intestines might be clinically relevant reservoirs of MRSA that should be taken into account during screening for such carriage during outbreak situations or when screening patients at risk.

Intestinal or perineal carriage as a risk factor for dissemination and infections

The perineum, as an area where *S. aureus* can colonize and multiply, was first recognized by Hare and Ridley [41], and heavy contamination from the perineum to the groin and upper parts of the thighs is often observed [42]. Both intestinal and perineal carriage have been implicated as important contributors to environmental dissemination of *S. aureus*. Patients with intestinal colonization of *S. aureus* may serve as an important source of transmission, since they often contaminate the adjacent environment. Masaki et al. [43] performed a prospective culture survey to investigate a possible relationship between *S. aureus* types colonizing the rectum and respiratory tract and *S. aureus* types isolated from the environment. They simultaneously detected in both patients and the environment several *S. aureus* types. This indicates a potential route of contamination of the hospital environment. It was also reported that

patients with intestinal and nasal colonization of *S. aureus* had higher frequencies of incontinence or diarrhea than patients without *S. aureus* colonization. This may significantly contribute to the observed trend toward increased contamination of environmental surfaces [44, 45]. The latter studies also substantiated that patients who have diarrheal stools and heavy gastro-intestinal colonization with MRSA are associated with significantly greater environmental MRSA contamination than patients without MRSA in their stools.

Data from early studies suggested an association between intestinal colonization and the occurrence of infections. For example, a study on recurrent furunculosis showed that 56% of the patients sampled had positive perineal cultures [46]. This suggested intestinal *S. aureus* carriage to be an infection risk factor, although nasal carriage was not precisely assessed for those patients. Hospitalized patients who reported developing *S. aureus* lesions on the buttocks and lower half of the abdomen and back often had the causative strain isolated from the perineum as well [47]. It was found that intensive care and liver transplant unit patients with both nasal and intestinal colonization had significantly increased rates of *S. aureus* infection of 40% compared with an infection rate of 18% in patients with nasal carriage without intestinal carriage [48]. On the basis of these data it was concluded that rectal carriage represents a potential reservoir and simultaneous nasal and rectal carriage portended a greater risk of *S. aureus* infections than nasal carriage alone in ICU and liver transplant unit patients. The same authors also proposed that intestinal colonization could be associated with an increased frequency of colonization of skin sites, which was confirmed in later studies [44]. It was found that patients with nasal and intestinal colonization were significantly more likely than those with nasal colonization only to have positive skin cultures. This group performed a prospective study involving 71 patients. The patients enrolled were divided into three groups: those without nasal or intestinal colonization, those with nasal colonization only, and those with both nasal and intestinal colonization. The development of *S. aureus* infections was significantly different among the three groups. Only 1 out of 32 patients without nasal or intestinal colonization developed an *S. aureus* infection. *S. aureus* infections developed more often in patients with stool colonization (8 out of 26) than in patients with only nasal colonization (2 out of 13). However, due to the small number of infected patients the power of this study was too limited to reach statistical significance. Significant differences in staphylococcal infection between patients with *S. aureus* in the stools and patients with negative stool cultures for *S. aureus* were documented [49]. In an 8-month prospective study of inpatients known to have vancomycin-resistant enterococci (VRE) colonization, none of the 14 patients with stool cultures negative for *S. aureus* developed an *S. aureus* infection in the hospital. In contrast, more than half of *S. aureus*-colonized patients had an *S. aureus* infection documented.

Eradication of intestinal carriage

Given its relatively high incidence, prevention of or therapy for intestinal carriage should be clinically beneficial. However, most studies are focused on the elimination of nasal rather than intestinal carriage. Nasal carriage eradication with mupirocin ointment has been studied frequently (recently reviewed by Van Rijen et al. [50]) and is generally considered to be highly effective, at least in the short term. However, reacquisition of carriage may occur from extranasal sites. Dupeyron et al. [51] monitored mupirocin treatment of 86 patients and found treatment failure in 22. For this group, the stool carriage rate was significantly higher and stool carriage upon admission was independently associated with reacquisition of nasal carriage. Conflicting results regarding the effects of nasal carriage eradication on the prevalence of MSSA/MRSA infections have been reported. Some authors showed significantly decreased rates of nosocomial infections [52, 53], whereas others did not [54, 55].

Mupirocin treatment may only be marginally effective in the eradication of multi-site carriage and, therefore, therapies based upon combinations of nasal, skin, and intestinal carriage eradication methods have more recently been exploited. The use of oral rifampin, for treatment of intestinal carriage of *S. aureus* for various patient populations and healthy people was reviewed by Falagas et al. [56, 57]. Rifampin, however, showed limited success in MRSA elimination. More novel treatment modalities for intestinal MRSA elimination to control transmission or subsequent infections, e.g., using oral vancomycin, have been described merely in uncontrolled or observational studies. Oral vancomycin treatment results were reported that showed that the eradication of MRSA intestinal carriage by enteral vancomycin in subsets of adult ICU patients [58–60] as well as in pediatric patients [61, 62] was effective, but had limited effect on the prevention of transmission. The results from prospective controlled studies of intestinal MRSA decolonization are urgently awaited.

Colonization of the intestinal tract by *S. aureus* may have another important clinical implication. The co-existence of *S. aureus* and VRE was reported in more than 50% of the American patients studied [49]. In this study, stool specimens were tested for VRE and *S. aureus* at enrollment (baseline) and weekly thereafter. Patients with at least three stool cultures were included in the study. Of the 37 patients who completed the study, all were colonized with VRE; 62%

were colonized with *S. aureus* on at least one occasion, and 60% were colonized persistently. Patients with stool cultures positive for *S. aureus* were colonized with MRSA strains in 87% of all cases. Warren et al. [63] screened stools and rectal samples from 878 ICU patients for VRE and MRSA. Of 485 VRE-positive patients, 83 (17%) also had intestinal carriage of MRSA. Furuno et al. [64] reported that out of 57 patients with both nasal MRSA carriage and intestinal VRE, 23 (40%) also had intestinal carriage of MRSA. These studies suggest that the intestinal tract could provide an important reservoir for the emergence of vancomycin-resistant *S. aureus* (VRSA) isolates

The emergence of the rectal carriage of CA-MRSA has been documented in a study in which *S. aureus* was detected in 507 of 2,963 vaginal/rectal cultures from late pregnancy cases (17%) [65]. Interestingly, 3% of the pregnant women had vaginal–rectal colonization of an epidemic CA-MRSA strain. A significant association between *S. aureus* colonization and Group B streptococcus (GBS) colonization was found. In a subsequent study this association was analyzed in more detail [66] and the significant association between MSSA and GBS was confirmed. Pregnant women with MSSA carriage were significantly more likely to have postpartum fever than those who were *S. aureus*-negative. Surprisingly, a significant negative association between CA-MRSA carriage and GBS carriage was observed. Apparently, when a certain bacterial species inhabits a given niche other species may not be able to colonize. In the case of the vaginal carriage of MRSA or MSSA such bacterial interference may lead to novel modes of intervention based on interference therapy of GBS once the microbial molecules involved have been identified.

Potential role of *S. aureus* in intestinal disease

How *S. aureus* causes intestinal infections is still ill-defined. The basic mechanisms are quite enigmatic and the etiological processes are just beginning to be identified. For instance, Froberg et al. [67] presented histo-pathological evidence for the existence of a specific *S. aureus*-induced pseudomembranous intestinal disease, distinct from that seen during *C. difficile* infection in an unusual case of simultaneous infection with *C. difficile* and MRSA. Whereas *C. difficile* induces colonic pseudomembranes, the MRSA infection induced loosely adherent pseudomembranes in the small bowel.

Intestinal carriage of *S. aureus* may impose a risk factor for intestinal infection. Antibiotic treatment can lead to the overgrowth of bacteria in the intestine and induce enteritis or AAD. The role of intestinal *S. aureus* as a causative agent for enteritis or AAD and as a risk factor for other infections gained renewed interest with the spreading of MRSA. MRSA has been suggested as a cause of AAD in hospitalized patients [68]. In this study *S. aureus* was the only identified pathogenic micro-organism to cause AAD in 47 patients and the presence of staphylococcal enterotoxin A was strongly associated with the development of diarrhea. A German study reported intestinal carriage of *S. aureus*, in the absence of *C. difficile* in 8% of patients with AAD [69]. Compelling evidence for the etiological role of MRSA in AAD was provided by excluding the involvement of *C. difficile*, numerous other bacterial pathogens and parasites, but also several enteric viruses in 11 patients with enterotoxin-producing MRSA intestinal carriage [70].

An extensive analysis of the prevalence of *C. difficile* and *S. aureus* in 2,727 stool samples of patients with diarrhea was performed. *C. difficile* grew from 148 specimens and 184 were positive for *C. difficile* toxin A/B analysis and altogether, a total of 252 stool samples were positively diagnosed with *C. difficile*. *S. aureus* was grown out of 198 fecal samples, of which 29 were identified as having MRSA [71]. In another study 10 MRSA-positive samples were detected out of 4,659 fecal samples [72]. Table 5 conclusively defines the interrelatedness between intestinal colonization by *S. aureus* and *C. difficile.*

Intestinal *S. aureus* colonization and disease development in infants and young children

In infants very high frequencies for intestinal *S. aureus* carriage were reported in early studies (reviewed by Williams [4], Table 6) and some of these suggested that acquisition of *S. aureus* occurred very early in life and probably as a consequence of nasal acquisition. Intestinal colonization in children was also studied more recently [73]. One hundred patients, below 16 years of age and attending the emergency department of a university hospital, who were analyzed for nasal and perineal carriage, included 20 *S. aureus*-colonized patients, of whom 2 (10%) had intestinal carriage in the absence of nasal carriage. Of this group, 17 patients (85%) had nasal carriage. Others studied *S. aureus* carriage in a child care center [74]. Of

Table 5 Frequency of detection of *C. difficile* and *S. aureus* in antibiotic-associated diarrhea (AAD) patients

Reference	Total	*C. difficile*, percentage (*n*)	*S. aureus*, percentage (*n*)
[68]	3,437	13 (460)	2 (60)
[70]	1,543	10 (159)	10 (151)
[69]	89	44 (39)	28 (25)
[72]	4,659	13 (591)	0.2 (10)
[71]	2,727	9 (252)	7 (198)

Table 6 *S. aureus* intestinal carriage in infants

References	Cases	Percentage	Method	Age
[92]	83	56	Stools	1–10 days
	22	100		2–6 months
	32	50		6–12 months
[76]	62	61	Stools	2 years
[73]	100	19	Perineal swabs	Hospitalized children up to 16 years
[78]	49	16	Rectal/stools	3 days
		57		1 week
		65		2 weeks
		65		4 weeks
		73		8 weeks
		73		6 months
		53		1 year
[98]	44	59	Stools	1 week
		61		1 month
		50		3 months
		39		6 months
		32		12 months
[77]	50	20	Rectal/stools	3 days
		40		1 week
		52		2 weeks
		60		4 weeks
		64		8 weeks
[79]	53	62	Rectal swabs	2 weeks
		70		4 weeks
[80]	324	13	Rectal swabs	3 days
		39		7 days
		52		14 days
		63		28 days
		72		2 months
		79		6 months

128 children who had swabs taken from nose, perineum, and throat, 8 (24%) had perineal carriage. Nasal and throat carriage frequency were higher with 15 (46%) and 22 (67%) respectively. An African study investigated the incidence of *S. aureus* in children aged 5 years and below suffering from sporadic diarrhea in Nigeria [75]. Out of 1,761 diarrheic fecal specimens collected, only 72 (4%) were positive for *S. aureus*.

Also, in more recent Swedish studies [76–79], high frequencies of intestinal *S. aureus* carriage during the first year of life were reported, and co-colonization of intestine and anterior nares with the same *S. aureus* strains, which were also found on the parents, suggested mother- to-child transmission. These studies were performed to test the hypothesis that development of allergic disease among children may be associated with differences in intestinal colonization patterns of *S. aureus*. Two-year-old allergic children from both Sweden and Estonia were reported to have significantly higher counts of *S. aureus* in the intestines than non-allergic children [76]. In a prospective follow-up study, significantly increased *S. aureus* intestinal prevalence at 6 months of age was found in a group of allergic children compared with the non-allergic group. An interesting correlation between intestinal colonization with *S. aureus* at 2 and 4 weeks of age and the development of food allergy was observed by Lundell et al. [79]. They also found a correlation between perinatal intestinal *S. aureus* colonization and expression levels of the soluble immune modulator CD14, but not the levels of CD83, and concluded that colonization with *S. aureus* might modulate the development of the neonatal immune system. This indicates an interrelatedness between factors involved in the host's immune response, early colonization, and development of allergic disease. Adlerberth et al. [80] studied the hypothesis that infantile intestinal colonization patterns may influence sensitization to food allergens and atopic eczema. They analyzed a birth cohort of more than 300 infants from three European countries with regard to relations between intestinal colonization patterns during the first year and the development of atopic eczema and sensitization at 18 months of age. They reported a nearly significant association ($p=0.06$) between early intestinal colonization with *S. aureus* and increased risk of atopic eczema. Kalliomaki et al. [81] recently observed that higher numbers of fecal *S. aureus* carriage at 6 and 12 months of age were associated with obesity in children.

Bisgaard et al. [82], who studied a Danish birth cohort of 411 infants, did not observe any correlation between neonatal airway colonization with *S. aureus* at 1 month of age and the development of childhood asthma. In contrast, for colonization with the classical otitis media bacteria *S. pneumonia*, *M. catarrhalis* and *H. influenzae* a significant association with increased persistent or acute wheezing and hospitalization for wheezing was observed. This seems to indicate a lack of influence of *S. aureus* colonization. However, since these studies were performed in a high-risk cohort, an alternative plausible interpretation of these data is that *S. aureus* to a greater extent than the other bacteria mentioned may modulate the neonatal immune system, and that the lower rates of wheezing associated with *S. aureus* colonization may actually reflect relative protection. This may be in line with observed differences in immune induction between gram-positive and gram-negative bacteria and the risk of childhood asthma [83]. The potential involvement of *S. aureus* enterotoxins (SE) in allergic diseases in early childhood by following 510 children from birth to 5 years of age was studied by Semic-Jusufagic et al. [84]. SE-mix-specific IgE, (SE-A, SE-C, and TSST-1) were measured to determine SE sensitization and correlated with atopic disease. Atopic children were nearly 4 times more SE-mix-sensitive than non-atopic children. Children with eczema were significantly more frequently SE-mix sensi-

tized than children without and the SE-mix sensitization rate increased significantly with increasing eczema severity. SE-mix sensitization was also significantly associated with current wheezing. Furthermore, SE-mix-sensitized children with wheezing had significantly higher airway reactivity than wheezing children who were not sensitized to SE-mix, which suggests that enterotoxins from *S. aureus* might be potential modifiers of childhood wheezing and eczema.

Intestinal MRSA in infants and young children at risk

Paired analysis of nasal and intestinal colonization during separate outbreaks of MRSA in children and newborns has been reported in a limited number of studies. After identification of a single case of MRSA infection, 128 children from a child care center were assessed for MSSA/MRSA carriage by perianal, nasal, and throat swabs [74]. This analysis identified an additional MRSA carrier only from the perianal swab, whereas the two other sites were negative. Singh et al. [85] found that during an MRSA outbreak at the neonatal intensive care unit of two hospitals, out of 373 infants analyzed, 24 were positive for MRSA. Of these, 7 (29%) had positive rectal cultures, of whom 1 (0.4%) was negative for nasal carriage. In 17 infants (71%) only the nasal culture was positive. Investigations during two MRSA outbreaks (one with a HA-MRSA and one with a CA-MRSA strain) were performed using paired nasal and intestinal screening [86]. Altogether, 1,792 newborns were screened and 50 were MRSA-positive. In the first hospital, out of 25 infants positively screened, 17 (71%) had nasal carriage and 5 (21%) had carriage in the rectum, all of whom also had nasal carriage. In the second hospital, 18 out of 25 positively screened (72%) had nasal carriage and 15 out of 25 infants (60%) had rectal carriage, of whom 3 (12%) did not have nasal carriage. The use of surveillance cultures of throat and rectal swabs in a pediatric intensive care unit is important [62]. Among 1,241 patients analyzed there were 29 MRSA carriers, of whom 14 (48%) had rectal carriage. Gustafsson et al. [87] described a study on MRSA carriage in 23 children adopted by Swedish families. Multiple swabs were taken from the perineum, nose, and other sites. MRSA was detected in 13 of the children. The perineum culture was positive at least once in 9 children (69%) and the nose was positive in 9 children (69%). Interestingly, 4 perineal MRSA carriers (31%) did not have nasal carriage.

Altogether, from these studies it can be deduced that of all the newborns or young children in whom MRSA was detected, 74% had nasal or throat carriage and 44% had intestinal carriage (Table 7). Moreover, 10% had intestinal carriage without nasal or throat carriage, which indicates that, in addition to nasal or throat carriage, the perineum or intestine also constitutes a colonization site with potential infection risk in newborns and young children.

Concluding remarks

Intestinal carriage of *S. aureus* occurs in a significant fraction of both healthy and diseased human individuals. For healthy adults and hospitalized adults at risk the incidence figure is 20%. For MRSA the average fraction of intestinal carriers amongst adult patients at risk is 9%. In young children the colonization of the intestines with *S. aureus* occurs at a very high frequency within the first 6 months of life, after which the frequency drops. For newborns and young children intestinal colonization with MRSA was detected in 1–2% of patients screened. This shows that the clinical impact of this phenomenon may be significant, which was corroborated in a number of studies that associated carriage and intestinal infection. Both MSSA and MRSA seem to successfully colonize the human intestines. This further emphasizes that care has to be taken: not only MSSA infections but also MRSA infection can result from intestinal carriage. Since MSSA and MRSA nasal carriage has been implicated to be a highly important risk factor for infections, the same will probably apply to intestinal carriage. Therefore, prospective controlled studies of intestinal carriage as a predictor of clinical infection need to be performed to determine the significance of this site of colonization. Prolonged intestinal carriage, also among personnel, can be an important factor

Table 7 Intestinal MRSA carriage in young children at risk

Reference	Total patients screened	Total positive carriers	Rectal MRSA	Nasal MRSA	Rectal without nasal
[74]	128	1	1	0	1
[85]	373	24	7	17	1
[86]	1,792	50	20	35	3
[62]	1,241	29	14	26[a]	3[a]
[87]	23	13	9	9	4
Totals	3,557	117	51	87	12
Percentage of total positive carriers			44%	74%	10%

[a] Throat swab analyzed instead of nasal swab

in the persistence of MRSA outbreaks in hospitals and can be a source of environmental contamination. The development of rapid molecular detection methods for MRSA carriage facilitates prophylaxis [88]. Nasally applied mupirocin very effectively eliminates nasal carriage and results in significant reductions in *S. aureus* infection rates. Mupirocin seems less effective for the elimination of intestinal carriage or other extra-nasal sites. Therefore, application of combined strategies, involving mupirocin in combination with oral antibiotics or other selective intestinal decontamination regiments, such as novel therapies based on polyclonal antibodies [89], may be more effective in cases of proven nasal and intestinal carriage. Because of the significant frequencies of intestinal carriage reported in a wide variety of patient groups and in healthy people it is recommended, in addition to nasal screening, to also include intestinal or perianal screening during surveillance.

Little is known on the age-related kinetics of intestinal carriage, but *S. aureus* seems to colonize the intestine of healthy newborns from very early in life onwards, and can be involved in the development of neonatal infectious disease. Later in life, intestinal carriage frequencies seem to drop. In concordance with nasal carriage, non-, intermittent and persistent intestinal carriage need to be defined in more detail. It is, therefore, of importance to determine whether specific variants of *S. aureus* are more proficient colonizers than others and which adhesion and virulence factors play a role in the transition from intestinal colonization to infection. Even more importantly, little is known on the environmental, bacteriological and physiological determinants of intestinal carriage. Preliminary data identify intestinal carriage as an infection risk factor and results from cohort studies suggest that there is interrelatedness among early intestinal colonization of *S. aureus*, the host's immune system, and the development of disease later in life. Additional research, however, will be needed to fully appreciate the importance of intestinal *S. aureus* colonization in association with infection.

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