What Is the Significance of *Staphylococcus aureus* Colonization in Hemodialysis Patients?

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Infection is the second leading cause of hospitalization and mortality among hemodialysis patients after cardiovascular disease [1]. *Staphylococcus aureus* (*S. aureus*) infections are extremely common in the hemodialysis population, and their incidence is 100-fold greater in the hemodialysis population than that observed in the general population [1]. These infections often result in major medical complications, prolonged hospital stays, and high economic costs [2]. The relationship between *S. aureus* colonization and infection remains a subject of ongoing debate. Numerous studies from around the world have documented a high prevalence of *S. aureus* colonization in hemodialysis (HD) patients (table 1), at a rate, which far exceeds that observed in the general population [1]. Factors contributing to this high rate of colonization include the patients' immunocompromised state, as well as their frequent hospitalizations and surgeries. The hemodialysis population is particularly susceptible to colonization with MRSA as a consequence of the frequent administration of antimicrobial agents, as well as regular exposure to health care systems [1].

Most published studies on *S. aureus* colonization in hemodialysis patients have obtained only nasal cultures (table 1), with the implicit assumption that nasal colonization is a representative of the colonization at other locations. The majority of these studies did not obtain cultures from other sites to confirm this hypothesis. Three studies documented extra-nasal *S. aureus* colonization in 32–40% of patients with nasal colonization [3–5]. None of these

studies, however, reported on the frequency of extra-nasal *S. aureus* colonization in the absence of nasal colonization. In the current issue of *Nephron*, Eells et al. investigated this question by simultaneously obtaining cultures from 100 hemodialysis patients from 3 body sites (nares, oropharynx, and inguinal) [6]. They observed *S. aureus* colonization in 42% of patients, including 36% with methicillin sensitive *S. aureus* (MSSA) and 6% with MRSA. These frequencies of *S. aureus* colonization are in line with those reported from other dialysis centers (table 1). The authors further noted that 10% of patients had colonization only in the nares, but not at the other two locations. Conversely, 14% of patients had colonization only at one or more extra-nasal locations, but not in the nares. In other words, one-third of patients (14/42) with documented *S. aureus* colonization would have been missed had the investigators obtained only nasal cultures. Importantly, genetic analysis of the 20 patients with *S. aureus* cultured from more than one site established that these contemporaneous cultures were from an identical strain, in agreement with previous studies suggesting clonality [5, 7].

There has been an ongoing interest in understanding the nature of the relationship between *S. aureus* colonization and systemic infection, the role of screening for colonization, and whether eradication of colonization in asymptomatic patients can prevent systemic infections. MRSA colonization in hemodialysis patients has been associated with a higher subsequent risk of infection and bacteremia [8] and a 2.46-fold higher risk of all-cause

Table 1. *S. aureus* colonization prevalence in outpatient hemodialysis patients

Reference	Screening sites	Number of patients	<i>S. aureus</i> prevalence (%)	MSSA (%)	MRSA (%)
Europe					
Schmid, 2013 [4]	N, T, S	289	–	–	11.8
Celik, 2011 [23]	N	184	28.8	23.4	4.9
Lederer, 2007 [24]	N	136	53	41	12
Duran, 2006 [25]	N	261	56.7	36	20.7
Mountricha, 2006 [26]	N	41	–	–	2.4
Koziol-Montewka, 2006 [27]	N	43	27.9	25.6	2.3
Pena, 2004 [5]	N, A, I	71	55	50.8	4.2
North America					
Eells, in press [6]	N, O, I	100	42	36	6.0
Alexander, 2011 [28]	N	157	30.6	24.2	6.4
Patel, 2011 [3]	N, A, V	102	–	–	16.7
Mermel, 2010 [29]	N	208	–	–	14.9
Pop-Vicas, 2008 [30]	N	67	–	–	4.5
Asia					
Uehara, 2013 [31]	N	112	25.9	17	8.9
Kang, 2012 [12]	N	116	17.3	12.1	5.2
	N	129	14.7	12.4	2.3
	N	306	–	–	9.5
Lai, 2011 [9]	N	84	36.9	9.5	27.4
Ghasemian, 2010 [32]	N	541	22.4	16.5	5.9
Wang, 2009 [33, 34]	N	509	21.8	19.4	2.4
Lu, 2008 [35]	N				
Africa					
Oumokhtar, 2013 [36]	N	70	42.9	41.5	1.4
Souly, 2011 [37]	N	54	44.4	38.9	5.6

Modified and adapted from Zacharioudakis et al. [8].

N = Nasal; A = axilla; V = vascular access site; O = oropharynx; I = inguinal; T = throat, S = skin (forehead, ears, axilla, hands); MSSA = methicillin-sensitive *S.aureus*. MRSA = methicillin-sensitive *S.aureus*.

mortality [9]. Patel et al. reported that 17.6% of patients colonized with MRSA subsequently developed a clinical infection [3]. Likewise, a recent meta-analysis reported that 19% of hemodialysis patients with MRSA colonization developed a clinical MRSA infection within 6–20 months [8].

Although MRSA colonization has been associated with clinical infection, it's less clear how it leads to infection. To look at it specifically, does colonization directly lead to the infection, or in general, is it simply a marker of severe comorbidities that independently make the patient more susceptible to infection? The answer to this question is quite relevant, as it would determine whether measures that treat *S. aureus* colonization actually reduce infection. Possible mechanisms with which *S. aureus* colonization might predispose to infection include (a) physical transfer from the endogenous site of colonization to the vascular access sites by contact, (b) protein malnutrition in this vulnerable population causing increased susceptibility to infections and colonization with resistant

strains [10], and (c) impaired cellular and cytokine response in colonized patients [11].

The study by Eells et al. [6] enhances our understanding of *S. aureus* colonization, but also raises some intriguing questions. For example, it's unclear why *S. aureus* colonization might occur at one body site, but not at another. Given that the nares and oropharynx are contiguous, what prevents oropharyngeal colonization in patients with nasal colonization? One possibility is that continuous oropharyngeal secretions have bactericidal properties that limit *S. aureus* colonization. It is also possible that the tonsillar ring forms a mechanical barrier that limits *S. aureus* transmission from the nares to the oropharynx. Another clinically relevant question is whether the application of a nasal antibiotic ointment to eradicate *S. aureus* colonization at that site also eradicates colonization at other body sites. If not, this may explain why prophylactic nasal mupirocin ointment can eradicate *S. aureus* nasal carriage without affecting *S. aureus* infection risks [12].

Studies have demonstrated that eradicating *S. aureus* carrier state can lower *S. aureus*-related infections but not overall infections [13–15]. Unfortunately, *S. aureus* colonization frequently recurs after the initial eradication with nasal mupirocin [5, 14, 15]. In addition, the emergence of mupirocin resistance during prolonged prophylactic use is a significant concern [16]. There is no compelling evidence that active clinical surveillance improves clinical outcomes [17] and routine infection prophylaxis with intranasal mupirocin has not been supported [15]. The Center for Disease Control has no specific MRSA screening recommendations for outpatient dialysis units. In summary, prophylactic treatment of *S. aureus* nasal colonization remains controversial owing to the uncertainty about its efficacy in preventing clinical infection, the frequent occurrence of recolonization, and the potential risk of selecting for resistant bacteria. Most studies evaluating the relationship of *S. aureus* and MRSA colonization with clinical infection in hemodialysis patients have been observational, and cannot establish a causal relationship. To justify changing the existing infection control guidelines, we desperately need randomized, double-blinded clinical trials comparing clinical infection rates in colonized patients receiving *S. aureus* nasal prophylaxis versus those receiving placebo.

A more effective approach for the prevention of clinical infection in patients with *S. aureus* bacteremia may be to apply antibiotic ointment at the likely site of commu-

nication from the body into the bloodstream. For example, in patients with tunneled hemodialysis dialysis catheters, the infecting organism is typically transmitted from the skin surrounding the exit site into the catheter lumen. Thus, the application of an appropriate antibiotic ointment at the catheter exit site may be more effective than nasal application. In support of this approach, two randomized clinical trials demonstrated a dramatic reduction of catheter-related bacteremia by applying mupirocin or polysporin at the catheter exit site after each dialysis session [18, 19]. Similarly, antibiotic or antimicrobial locks that decolonize the vascular access catheter lumen have also prevented systemic infections [20]. Although short-term studies have demonstrated the effectiveness of these approaches, longer follow-ups have raised concerns about the selection of resistant organisms, including mupirocin-resistant *Staphylococcus* [16], gentamicin-resistant *Staphylococcus* [21], and yeast [22]. Use of non-antibiotic antimicrobial catheter locks may obviate this risk. In conclusion, strategies aimed at infection prevention and prophylaxis at vascular access sites that are the potential sites of *S. aureus* transmission into the bloodstream may be more effective than decolonization at a more distant anatomic site. Implementation of these strategies would substantially reduce the frequency of serious *S. aureus* infections in hemodialysis patients, and thereby decrease mortality, hospitalizations, and health care costs in this patient population.

References

- 1 United States Renal Data System, 2014 annual data report: An overview of the epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2014.
- 2 Vandecasteele SJ, Boelaert JR, De Vriese AS: Staphylococcus aureus infections in hemodialysis: what a nephrologist should know. Clin J Am Soc Nephrol 2009;4:1388–1400.
- 3 Patel G, Jenkins SG, Mediavilla JR, et al: Clinical and molecular epidemiology of methicillin-resistant Staphylococcus aureus among patients in an ambulatory hemodialysis center. Infect Control Hosp Epidemiol 2011;32:881–888.
- 4 Schmid H, Romanos A, Schiff H, Lederer SR: Persistent nasal methicillin-resistant staphylococcus aureus carriage in hemodialysis outpatients: a predictor of worse outcome. BMC Nephrol 2013;14:93.
- 5 Peña C, Fernández-Sabe N, Domínguez MA, et al: Staphylococcus aureus nasal carriage in patients on haemodialysis: role of cutaneous colonization. J Hosp Infect 2004;58:20–27.
- 6 Eells SJ, Kalantar-Zadeh K, Bolaris MA, May L, Miller LG: Body site Staphylococcus aureus colonization among maintenance hemodialysis patients. Nephron 2015;129:79–83.
- 7 Boelaert JR, Van Landuyt HW, Gordts BZ, et al: Nasal and cutaneous carriage of Staphylococcus aureus in hemodialysis patients: the effect of nasal mupirocin. Infect Control Hosp Epidemiol 1996;17:809–811.
- 8 Zacharioudakis IM, Zervou FN, Ziakas PD, Mylonakis E: Meta-analysis of methicillin-resistant Staphylococcus aureus colonization and risk of infection in dialysis patients. J Am Soc Nephrol 2014;25:2131–2141.
- 9 Lai CF, Liao CH, Pai MF, et al: Nasal carriage of methicillin-resistant Staphylococcus aureus is associated with higher all-cause mortality in hemodialysis patients. Clin J Am Soc Nephrol 2011;6:167–174.
- 10 Hadley AC, Karchmer TB, Russell GB, McBride DG, Freedman BI: The prevalence of resistant bacterial colonization in chronic hemodialysis patients. Am J Nephrol 2007;27:352–359.
- 11 Kozioł-Montewka M, Chudnicka A, Ksiazek A, Majdan M: Rate of Staphylococcus aureus nasal carriage in immunocompromised patients receiving haemodialysis treatment. Int J Antimicrob Agents 2001;18:193–196.
- 12 Kang YC, Tai WC, Yu CC, Kang JH, Huang YC: Methicillin-resistant Staphylococcus aureus nasal carriage among patients receiving hemodialysis in Taiwan: prevalence rate, molecular characterization and de-colonization. BMC Infect Dis 2012;12:284.
- 13 Kluytmans JA, Wertheim HF: Nasal carriage of Staphylococcus aureus and prevention of nosocomial infections. Infection 2005;33:3–8.
- 14 Herwaldt LA: Reduction of Staphylococcus aureus nasal carriage and infection in dialysis patients. J Hosp Infect 1998;40(suppl B):S13–S23.
- 15 Laupland KB, Conly JM: Treatment of Staphylococcus aureus colonization and prophylaxis for infection with topical intranasal mupirocin: an evidence-based review. Clin Infect Dis 2003;37:933–938.

- 16 Pérez-Fontán M, Rosales M, Rodríguez-Carmona A, Falcón TG, Valdés F: Mupirocin resistance after long-term use for *Staphylococcus aureus* colonization in patients undergoing chronic peritoneal dialysis. *Am J Kidney Dis* 2002;39:337–341.
- 17 Weber SG, Huang SS, Oriola S, et al: Legislative mandates for use of active surveillance cultures to screen for methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci: position statement from the Joint SHEA and APIC task force. *Am J Infect Control* 2007;35:73–85.
- 18 Lok CE, Stanley KE, Hux JE, Richardson R, Tobe SW, Conly J: Hemodialysis infection prevention with polysporin ointment. *J Am Soc Nephrol* 2003;14:169–179.
- 19 Johnson DW, MacGinley R, Kay TD, et al: A randomized controlled trial of topical exit site mupirocin application in patients with tunnelled, cuffed haemodialysis catheters. *Nephrol Dial Transplant* 2002;17:1802–1807.
- 20 Aslam S, Vaida F, Ritter M, Mehta RL: Systematic review and meta-analysis on management of hemodialysis catheter-related bacteremia. *J Am Soc Nephrol* 2014;25:2927–2941.
- 21 Landry DL, Braden GL, Gobeille SL, Haessler SD, Vaidya CK, Sweet SJ: Emergence of gentamicin-resistant bacteremia in hemodialysis patients receiving gentamicin lock catheter prophylaxis. *Clin J Am Soc Nephrol* 2010;5:1799–1804.
- 22 Oliveira L, Graham J, Lok C, Macfarlane S, Zimmerman D: Risk factors for yeast superinfection in the treatment of suspected exit site infections: a case-control study. *J Vasc Access* 2008;9:35–38.
- 23 Celik G, Gülcan A, Dikici N, Gülcan E: Prevalence of nasal *Staphylococcus aureus* carriage in the patients undergoing hemodialysis and evaluation of risk factors and laboratory parameters. *Ren Fail* 2011;33:494–498.
- 24 Lederer SR, Riedelsdorf G, Schiffel H: Nasal carriage of methicillin resistant *Staphylococcus aureus*: the prevalence, patients at risk and the effect of elimination on outcomes among out-clinic haemodialysis patients. *Eur J Med Res* 2007;12:284–288.
- 25 Duran N, Ocak S, Eskiocak AF: *Staphylococcus aureus* nasal carriage among the diabetic and non-diabetic haemodialysis patients. *Int J Clin Pract* 2006;60:1204–1209.
- 26 Mountricha A, Platsouka E, Pappas C, et al: *S. aureus* nasal carriage among hemodialysis (HD) patients. *Clin Nephrol* 2006;65:229–230.
- 27 Kozioł-Montewka M, Szczepanik A, Baranowicz I, Józwiak L, Ksiazek A, Kaczor D: The investigation of *Staphylococcus aureus* and coagulase-negative staphylococci nasal carriage among patients undergoing haemodialysis. *Microbiol Res* 2006;161:281–287.
- 28 Alexander EL, Morgan DJ, Kesh S, et al: Prevalence, persistence, and microbiology of *Staphylococcus aureus* nasal carriage among hemodialysis outpatients at a major New York Hospital. *Diagn Microbiol Infect Dis* 2011;70:37–44.
- 29 Mermel LA, Eells SJ, Acharya MK, et al: Quantitative analysis and molecular fingerprinting of methicillin-resistant *Staphylococcus aureus* nasal colonization in different patient populations: a prospective, multicenter study. *Infect Control Hosp Epidemiol* 2010;31:592–597.
- 30 Pop-Vicas A, Strom J, Stanley K, D'Agata EM: Multidrug-resistant gram-negative bacteria among patients who require chronic hemodialysis. *Clin J Am Soc Nephrol* 2008;3:752–758.
- 31 Uehara Y, Kuwahara-Arai K, Hori S, Kikuchi K, Yanai M, Hiramatsu K: Investigation of nasal methicillin-resistant *Staphylococcus aureus* carriage in a haemodialysis clinic in Japan. *J Hosp Infect* 2013;84:81–84.
- 32 Ghasemian R, Najafi N, Makhloogh A, Khademloo M: Frequency of nasal carriage of *Staphylococcus aureus* and its antimicrobial resistance pattern in patients on hemodialysis. *Iran J Kidney Dis* 2010;4:218–222.
- 33 Wang CY, Wu VC, Chen YM, Su CT, Wu KD, Hsueh PR: Nasal carriage of methicillin-resistant *Staphylococcus aureus* among patients with end-stage renal disease. *Infect Control Hosp Epidemiol* 2009;30:93–94.
- 34 Wang CY, Wu VC, Wang WJ, et al: Risk factors for nasal carriage of methicillin-resistant *Staphylococcus aureus* among patients with end-stage renal disease in Taiwan. *J Formos Med Assoc* 2012;111:14–18.
- 35 Lu PL, Tsai JC, Chiu YW, et al: Methicillin-resistant *Staphylococcus aureus* carriage, infection and transmission in dialysis patients, healthcare workers and their family members. *Nephrol Dial Transplant* 2008;23:1659–1665.
- 36 Oumokhtar B, Elazhari M, Timinouni M, et al: *Staphylococcus aureus* nasal carriage in a Moroccan dialysis center and isolates characterization. *Hemodial Int* 2013;17:542–547.
- 37 Souly K, Ait el kadi M, Lahmadi K, et al: Epidemiology and prevention of *Staphylococcus aureus* nasal carriage in hemodialyzed patients. *Med Mal Infect* 2011;41:469–474.