Life-threatening Skin Disorders Treated in the Burn Center

Impact of Health care–associated Infections on Length of Stay, Survival, and Hospital Charges

Steven J. Hermiz, MD[a], Paul Diegidio, MD[b], Shiara Ortiz-Pujols, MD[b], Roja Garimella, BS[c], David J. Weber, MD, MPH[d], David van Duin, MD, PhD[d], Charles Scott Hultman, MD, MBA[b,*]

KEYWORDS

• Stevens-Johnson syndrome • Toxic epidermal necrolysis • Life-threatening skin disorders • Hospital-acquired infections • Health care–associated infections

KEY POINTS

- Patients with life-threatening skin disorders, including those with Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), are best treated in a burn center, because of the availability of subspecialists in surgical critical care, wound management, and rehabilitation.
- Critically ill patients with acute skin disorders have an increased need for intensive care unit care, compared with the SJS-TEN cohort, but both groups have similar length of hospital stay, survival, and incidence of hospital-acquired infections.
- Hospital-acquired infections, which are theoretically preventable, significantly increase both mortality and hospital charges, to an even greater degree, in the SJS-TEN subgroup.

INTRODUCTION

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are part of a clinical syndrome that represents a medication-induced desquamation disorder. In 1922, Drs Stevens and Johnson first described SJS as an acute mucocutaneous syndrome presenting in 2 young boys.[1–3] Alan Lyell later presented 4 patients in 1956 with a cutaneous eruption and coined the term TEN.[1,2,4–7]

SJS-TEN are the 2 most common adverse drug reactions in hospitalized patients. SJS-TEN are grouped along with acute generalized exanthematous pustulosis, drug-induced hypersensitivity syndrome, and drug reaction with eosinophilia and

Funding Sources: None.
Conflicts of Interest: None.
[a] Department of Surgery, University of South Carolina School of Medicine, Columbia, SC 29209, USA; [b] Department of Surgery, University of North Carolina School of Medicine, 7038 Burnett-Womack, Campus Box 7195, Chapel Hill, NC 27599, USA; [c] Alpert Medical School, Brown University, Providence, RI 02903, USA; [d] Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, NC 27599, USA
* Corresponding author.
E-mail address: cshult@med.unc.edu

Clin Plastic Surg 44 (2017) 597–602
http://dx.doi.org/10.1016/j.cps.2017.02.006

systemic symptoms (DRESS), to encompass severe cutaneous adverse reactions.[8,9] The two entities are distinguished from each other by disease severity, which is characterized by the extent of detachment of epidermis and erosions of mucous membranes.[2,4,6,8–14] The total body surface area (TBSA) involved in SJS is less than 10%, 10% to 30% in SJS-TEN overlap, and greater than 30% in TEN.[1,2,6,8–13,15,16] In more than 95% of TEN cases, the mucous membranes involved include the eyes, lips, mouth, pharynx, trachea, bronchi, vulva, glans penis, urethra, and anus.[1,8,9,11,12]

Patients admitted to a burn center with a potential diagnosis along the SJS/TEN spectrum often have high hospital morbidity and mortality. However, little is known about patients admitted to a burn center with life threatening skin disorders (LTSDs) not caused by SJS/TEN. This group includes severe rashes, nonhealing wounds, erythema multiforme, and unknown skin lesions requiring hospitalization for critical care, skin biopsy, and aggressive wound care.

This article compares and contrasts patients admitted to a single burn center and diagnosed with LTSD or SJS/TENS, focusing on intensive care unit (ICU) care, hospital charges, cost, and mortality. Furthermore, the impact of hospital-acquired infections (HAIs; also known as health care–associated infections) on these patient outcomes is assessed.

METHODS

Patient Population

Over a 10-year period from 2003 to 2013, 445 patients were admitted to the North Carolina Jaycee Burn Center with life-threatening dermatologic conditions other than thermal injury. The University of North Carolina (UNC) Health Care System is a conglomerate of health care providers and organizations that includes the School of Medicine, UNC Hospitals in Chapel Hill, and multiple hospitals and physician practices across the state of North Carolina.

Study Design

The authors conducted a retrospective, descriptive review of the 445 patients who had a diagnosis of a dermatologic condition requiring hospitalization in our burn center. Patients were identified from a prospectively managed database, and a post-hoc analysis was performed. These charts, divided into SJS-TEN and LTSD, were cross-referenced with the hospital-wide infection control database to identify patients who developed HAIs. We used the definitions developed by the Centers for Disease Control and Prevention National Healthcare Safety Network to accurately and consistently diagnose HAIs.

Statistical Methods

Continuous discrete data (age, TBSA involved, length of stay, ventilation days, ICU days, HAI, mortality, mortality with HAI, cost, cost with HAI, catheter-associated urinary tract infection [CAUTI], blood stream infections [BSIs], and urinary tract infections [UTI]) were compared using either 2-tailed *t*-test or χ^2 analysis for nominal and categorical variables, respectively. Statistical significance was assigned to *P* values less than .05.

Study Approval

The UNC Biomedical Institutional Review Board approved this project as Institutional Review Board study number 14-1789, under the title Anticipating Changes in Bundled Payments For the Treatment of Patients with Acute, Life-threatening Dermatologic Emergencies, Through Prevention of Healthcare Associated Infections.

Data Points

The charts of 445 patients with dermatologic conditions requiring hospitalization were queried for age, gender, and TBSA involved. Main outcome measures included length of hospital stay, ventilation days, ICU days, and overall cost, generated by the facility. Complications assessed included HAIs, inpatient mortality, CAUTI, BSI, and UTI. Inpatient mortality associated with HAIs and cost associated with HAIs were also calculated.

RESULTS

Patient Demographics

Between 2003 and 2013, 445 patients were identified with dermatologic emergencies who were admitted to our burn unit. There were 316 patients in the LTSD group and 129 patients in the SJS-TEN cohort. The mean age in the LTSD group was 52.8 $\pm$ 23.3 years and 48.3 $\pm$ 22.6 years in the SJS-TEN group. Patients presenting with LTSD were more likely to be female compared with patients with SJS-TEN (78.4% vs 58.1%; $P = .04$). There was no difference in TBSA involvement between the two groups (19.3% vs 21.2%; $P = .61$).

Cause

Patients with LTSDs (n = 316) included more than 30 different diagnostic groups, with the top 11 involving drug rash (n = 43), exanthematous pustulosis (n = 22), staphylococcal scalded skin syndrome (n = 13), necrotizing fasciitis (n = 12), erythema multiforme (n = 12), pemphigoid

(n = 12), contact dermatitis (n = 10), exfoliative psoriasis (n = 8), leukocytoclastic vasculitis dermatitis (n = 6), viral rash (n = 5), and erosive pustular dermatitis (n = 4). Although physical examination may help form a clinical diagnosis, all patients underwent skin biopsy to determine the exact dermatologic diagnosis. An additional 45 patients (23.2%) were determined to have the following diagnoses: cutaneous lupus flare, cellulitis, impetigo, linear immunoglobulin A dermatosis, traumatic crush wound, DRESS syndrome, scald injury, acute spongiotic dermatitis (eczema), calciphylaxis, suppurative hidradenitis, exfoliative xeroderma, chronic wound after burn, solar purpura, erysipelas, purpura fulminans, dermatomyositis, Sweet syndrome, lichen planus, soft tissue necrosis caused by Levophed, necrolytic migratory erythema, penile skin eruption, pressure ulcer, degloving, thrombotic skin necrosis, and fungal rash (each category with 1–3 patients).

Of the 129 patients with SJS-TEN spectrum, the inciting drug was identified in 121 (93.8%). The most common pharmacologic category was an antimicrobial agent, which included antibacterials (n = 50), antivirals (n = 2), antimycobacterials (n = 2), and antifungals (n = 1). The next most common categories were anticonvulsants (n = 7), nonsteroidal antiinflammatory drugs (n = 4), and antigout agents (n = 3). Specific drugs included Bactrim, Lamictal, capsaicin, azithromycin, allopurinol, ibuprofen and naproxen, acetaminophen, cephalosporins, vancomycin, Dramamine, clindamycin, acyclovir, Tamiflu, doxycycline, Dilantin, fluoroquinolone, penicillin, Macrobid, chlorphenamine, dapsone, Plaquenil, caspofungin, Lopid, and Tegretol. Bactrim, which is a combination of sulfamethoxazole and trimethoprim, was observed in 23 cases (17.8%).

Main Outcome Measures

The mean length of stay was 28.16 days (standard deviation [SD], 27.2 days) for the LTSD group and 22.5 days (SD, 24.5 days) for the SJS-TEN group (P = .19). Patients in the LTSD group had greater mean number of ventilator days compared with patients in the SJS-TEN group (16.39 vs 11.11 days; P<.01). The LTSD group had greater mean number of ICU days compared with the SJS-TEN group (25.35 vs 16.57 days; P<.01). The total hospital cost was higher for the LTSD group than for the SJS-TEN group ($179,316 vs $167,363; P = .01) (**Table 1**).

Complications

The LTSD group had a 19.9% inpatient mortality compared with a 20.9% mortality for the SJS-TEN group, which was not statistically significant (P = .75). A total of 69 patients with LTSD (21.8%) and 38 patients with SJS-TEN (29.5%) had an HAI (P = .08) (**Figs. 1** and **2**). Twelve patients (3.8%) in the LTSD group had a CAUTI, compared with 11 patients (8.5%) in the SJS-TEN group (P = .04). One patient (0.3%) in the LTSD group and 3 patients (2.3%) in the SJS-TEN group had a BSI (non–central line related)

Table 1
Patient variables

	LTSD n = 316	SJS-TEN n = 129	*P* Value
Age	52.8 y (23.3 y)	48.3 y (22.6 y)	.98
Female	78.4%	58.1%	.04
TBSA	19.3% (27.1%)	21.2% (27.0%)	.61
LOS	28.16 d (27.2 d)	22.5 d (24.5 d)	.19
Use of Ventilator	16.39 d (161 d)	11.11 d (24.07 d)	<.01
ICU Stay	25.35 d (197 d)	16.57 d (24.77 d)	<.01
HAIs	21.8%	29.5%	.08
Mortality	19.9%	20.9%	.75
Mortality with HAI	37%	66%	.25, .01
Cost	$179,316	$167,363	.01
Cost with HAI	$296,984	$468,542	.001, .001
CAUTI	3.8%	8.5%	.04
BSI	0.3%	2.3%	.04
UTI	3.5%	0%	.03

Abbreviation: LOS, length of stay.

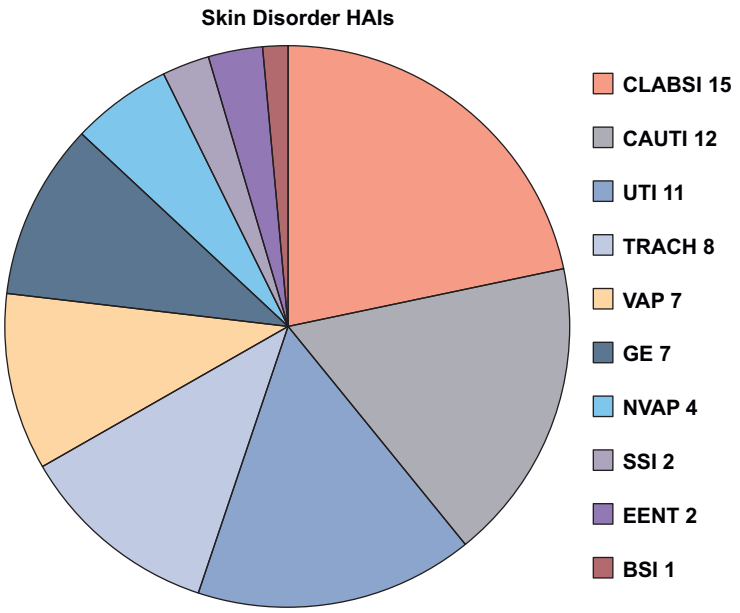

Fig. 1. HAIs in the LTSD group. BSIs are non–central line related, and UTIs are non–catheter related. CLABSI, central line–associated blood stream infection; GE, gastroenteritis (usually *Clostridium difficile*); NVAP, non–ventilator-associated pneumonia; SSI, surgical site infection; Trach, tracheobronchitis; VAP, ventilator-associated pneumonia.

(*P* = .04). Eleven patients had a UTI (non–catheter related) in the LTSD group and no patients had a UTI (non–catheter related) in the SJS-TEN group (*P* = .03). The mortality for patients in the LTSD group with an HAI was 37% (*P* = .25), compared with 66% (*P* = .01) in the SJS-TEN group. The total hospital cost accrued for patients in the LTSD group with HAIs was $296,984 (*P* = .001) and $468,542 (*P* = .001) for the SJS-TEN group.

The most common HAI pathogens in the LTSD group, in descending order, were *Pseudomonas aeruginosa*, *Candida*, *Acinetobacter*, *Clostridium difficile*, and methicillin-resistant *Staphylococcus aureus* (MRSA). The most common HAI pathogens in the SJS-TEN group, in descending order, were

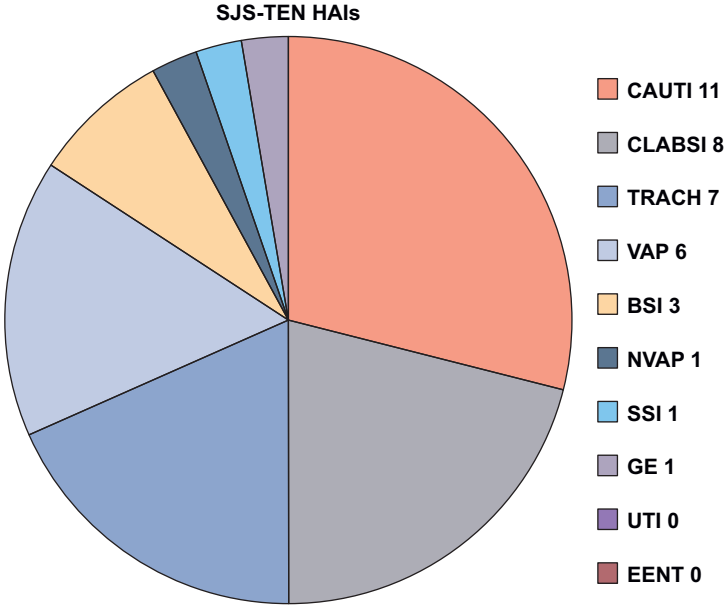

Fig. 2. HAIs in the SJS-TEN group.

MRSA, *P aeruginosa*, *Candida*, *Stenotrophomonas*, and *Acinetobacter*.

SUMMARY

This article shares our experience with 445 patients presenting with dermatologic conditions requiring hospitalization in our burn center over a 10-year period. It compares patients with LTSDs and SJS-TEN, using such outcome metrics as length of stay, costs, mortality, and the incidence of HAIs. Patients with LTSD had significantly more ICU and ventilator days compared with patients with SJS-TEN. When HAIs were present, both groups had a significant increase in hospital charges, and patients with SJS-TEN had increased inpatient mortality. The two cohorts did not differ in terms of percentage TBSA, overall inpatient mortality, or incidence of HAIs. Patients with LTSD were also significantly more likely to be female, and they had a higher incidence of UTI (non–catheter related) compared with the SJS-TEN cohort. In contrast, patients with LTSD were less likely to develop a BSI (non–central line related) or CAUTI than patients with SJS-TEN.

LTSDs can be congenital, hereditary, or acquired cutaneous reactions. Acquired cutaneous reactions include meningococcal septicemia skin eruption, necrotizing fasciitis, staphylococcal scalded skin syndrome, erythema multiforme, purpura fulminans, pemphigoid, TEN, and SJS.[2,17] The incidence of SJS-TEN is approximately 1 to 2 new cases per million per year,[1,2,4,6,7,10,11,13,15,18,19] and the average mortality ranges from 25% to 40%.[5,6,9,11–13,15,16]

The average mortality for both the LTSD and SJS-TEN groups was lower than these reported figures, at 19.9% and 20.9%, respectively. Palmieri and colleagues[12] conducted a multicenter study involving 15 regional burn centers and showed that survival rate was significantly higher in patients who were transferred to a burn unit within 7 days after disease onset, compared with patients transferred after 7 days.[1,20] A delay in referral was associated with prolonged hospital stay and increased mortality.[4,6,9,11,12,15]

HAIs negatively affect morbidity, mortality, and economic cost. Infection is the main cause of mortality among patients with extensive burns and LTSDs.[21] The development of an HAI was associated with an increase in mortality from 19.9% to 37% in the LTSD group, and an increase in mortality from 20.9% to 66% in the SJS-TEN group. Similar to other published studies, BSIs that were non–central line related were more common in the SJS-TEN group, with a reported incidence in the literature of 15.5 per 1000 patient days.[15] The most common pathogens for BSI were MRSA and *P aeruginosa*, which are the most common pathogens identified in the literature.[5,11,15] Revuz and colleagues[5] reported that these 2 pathogens were the primary cause of death in 87 patients with TEN, resulting in hospital mortality of 25%.[11,15]

The economic cost of HAIs has been a significant financial burden to health care systems. For example, an episode of symptomatic UTI adds approximately $676 to hospital costs. Primary BSIs increase patient charges by $3517 per episode, and in one study yielded a mean difference of $34,508 compared with uninfected patients.[22] The annual cost of nosocomial UTIs in the United States ranges from $424 million to $451 million. The direct cost consists of the increased length of hospital stay, extra tests, and treatment required.[23,24] The Study of the Efficacy of Nosocomial Infection Control (SENIC) reported that HAIs affected approximately 6% of admitted patients in US hospitals.[23,25] The World Health Organization estimated the HAI burden to be $1.4 billion per annum.[23,25] Hospital-acquired BSIs not only cause morbidity and mortality; they add significant economic costs, ranging from $3061 to $40,000.[26]

Medicare's nonpayment policy for hospital-acquired conditions prompted a reduction in the rate of central line–associated bloodstream inflections by 11% and CAUTI by 10%.[25] Catheter-related bacteremia costs $2900 per episode. The total cost for nosocomial and community-acquired UTI is approximately $2 billion.[27] If a similar trend in Medicare nonpayment occurs for HAIs, this will pose tremendous challenges to health care systems, which have operating margins that may not be able to accommodate this decrease in reimbursement.

Despite receiving care at an American Burn Association (ABA)–verified burn center, patients in the LTSD and SJS-TEN cohorts developed HAIs at an incidence of 21.8% and 29.5%, respectively. Nonpayments for HAIs, in this setting, result in significant financial strain for all health care systems. The estimated annual cost of skin disease is $29.1 billion in direct medical costs and $10.2 billion in lost productivity costs. The economic burden on quality of life was estimated to be $56.2 billion.[28] Clearly, preventing or reducing HAIs in patients with acute LTSDs, regardless of cause, should become a primary goal of all burn centers.

Clinicians taking care of patients with SJS-TEN, as well as those with other LTSDs, should be aware of the profoundly negative impact of HAIs on number of ventilator days, length of ICU stay, length of hospitalization, and survival. With bundled payments on the horizon, and potential nonpayment of HAI complications, health care facilities may not be able to cover the cost of providing care to this group of patients, who are best managed by burn centers.

REFERENCES

1. Harr T, French LE. Toxic epidermal necrolysis and Stevens-Johnson syndrome. Orphanet J Rare Dis 2010;5(39):1–11.
2. Ugburo AO. A 12-year retrospective study of non-burn skin loss(burn-like syndromes) at a tertiary burns unit in a developing country. Burns 2008; 34(5):637–43.
3. Auquier-Durant A, Mockenhaupt M, Naldi L, et al. Correlations between clinical patterns and causes of erythema multiforme majus, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Arch Dermatol 2002;138:1019–24.
4. Neff P, Meuli-Simmen C, Kempf W, et al. Lyell syndrome revisited: analysis of 18 cases of severe bullous skin disease in a burns unit. Br J Plast Surg 2005;58:73–80.
5. Revuz J, Penso D, Roujeau JC, et al. Toxic epidermal necrolysis: clinical findings and prognosis factors in 87 patients. Arch Dermatol 1987; 123:1160–5.
6. Struck MF, Hilbert P, Mockenhaupt M, et al. Severe cutaneous adverse reactions: emergency approach to non-burn epidermolytic syndromes. Intensive Care Med 2010;36(1):22–32.
7. Forman R, Koren G, Shear NH. Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis in children: a review of 10 years' experience. Drug Saf 2003;25(13):955–72.
8. Mockenhaupt M. Stevens-Johnson syndrome and toxic epidermal necrolysis: clinical patters, diagnostic considerations, etiology, and therapeutic management. Semin Cutan Med Surg 2014; 33(1):10–6.
9. Gerdts B, Vloemans AF, Kreis RW. Toxic epidermal necrolysis: 15 years' experience in a Dutch burns centre. J Eur Acad Dermatol Venereol 2007;21(6): 781–8.
10. Bastuji-Garin S, Fouchard N, Bertocchi M, et al. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. J Invest Dermatol 2000; 115(2):149–53.
11. Downey A, Jackson C, Harun N, et al. Toxic epidermal necrolysis: review of pathogenesis and management. J Am Acad Dermatol 2012;66(6):995–1003.
12. Palmieri TL, Greenhalgh DG, Saffle JR, et al. A multicenter review of toxic epidermal necrolysis treated in U.S. burn centers at the end of the twentieth century. J Burn Care Rehabil 2002;23(2):87–96.
13. Schultz JT, Sheridan RL, Ryan CM, et al. A 10-year experience with toxic epidermal necrolysis. J Burn Care Rehabil 2000;21(3):199–204.
14. Tay YK, Huff JC, Weston WL, et al. *Mycoplasma pneumoniae* infection is associated with Stevens-Johnson syndrome, not erythema multiforme. J Am Acad Dermatol 1996;35(5):757–60.
15. de Prost N, Ingen-Housz-Oro S, Duong TA, et al. Bacteremia in Stevens-Johnson syndrome and toxic necrolysis: epidemiology, risk factors, and predictive value of skin cultures. Medicine (Baltimore) 2010;89(1):28–36.
16. Yarborough DR. Experience with toxic epidermal necrolysis treated in a burn center. J Burn Care Rehabil 1996;17(1):30–3.
17. Atiyeh BS, Dham R, Yassin MF, et al. Treatment of toxic epidermal necrolysis with moisture-retentive ointment: a case report and review of the literature. Dermatol Surg 2003;29(2):185–8.
18. Nandha R, Gupta A, Hashmi A. Cutaneous adverse drug reactions in a tertiary care teaching hospital: a North Indian perspective. Int J Appl Basic Med Res 2011;1(1):50–3.
19. George SM, Harrison DA, Welch CA, et al. Dermatological conditions in intensive care: a secondary analysis of the Intensive Care National Audit and Research Centre (ICNARC) case mix programme database. Crit Care 2008;12(Suppl 1):S1.
20. Zajiceck R, Pintar D, Broz L, et al. Toxic epidermal necrolysis and Stevens-Johnson syndrome at the Prague Burn Centre 1998-2008. J Eur Acad Dermatol Venereol 2012;26(5):639–43.
21. Santucci SG, Gobara S, Santos CR, et al. Infections in a burn intensive care unit: experience of seven years. J Hosp Infect 2003;53:6–13.
22. DiGiovine C, Chenoweth C, Watts C, et al. The attributable mortality and costs of primary nosocomial bloodstream infections in the intensive care unit. Am J Respir Crit Care Med 1999;160:976–81.
23. Coello R, Glenister H, Fereres J, et al. The cost of infection in surgical patients: a case-control study. J Hosp Infect 1993;25(4):239–50.
24. Hassan M, Tuckman HP, Patrick RH, et al. Cost of hospital-acquired infection. Hosp Top 2010;88(3):82–9.
25. Waters TM, Daniels MJ, Bazzoli GJ, et al. Effect of Medicare's nonpayment for hospital-acquired conditions: lessons for future policy. JAMA Intern Med 2015;175(3):347–54.
26. Orsi GB, Di Stefano L, Noah N. Hospital-acquired, laboratory-confirmed bloodstream infection: increased hospital stay and direct costs. Infect Control Hosp Epidemiol 2002;23(4):190–7.
27. Foxman B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. Dis Mon 2003;49(2):53–70.
28. Bickers DR, Lim HW, Margolis D, et al. The burden of skin diseases: 2004 a joint project of the American Academy of Dermatology Association and the Society for Investigative Dermatology. J Am Acad Dermatol 2006;55(3):490–500.