



New Developments in Bacterial, Viral, and Fungal Cutaneous Infections

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Abstract

Purpose of Review This review highlights clinically relevant updates to common and significant bacterial, viral, and fungal cutaneous infection within the past 5 years. Recent developments are presented so that the clinician may provide evidence-based, high-quality patient care.

Recent Findings New resistance patterns in cutaneous pathogens have recently emerged as a result of inappropriate antimicrobial use. Several new FDA-approved antimicrobials have been approved to treat such infections, including multi-drug resistant pathogens. Several organizational guidelines for cutaneous infection management have been updated with new recommendations for screening, diagnostic, and treatment strategies.

Summary Clinicians should be aware of the most recent evidence and guidelines for the management of cutaneous infections in order to reduce the emergence of antimicrobial resistance and most effectively treat their patients.

Keywords Cutaneous infections · Infectious dermatology · Developments · Antibiotic resistance · Guideline updates · Emerging infections

Introduction

Skin and soft tissue infections (SSTIs) are one of the most common types of infection with diverse etiologies and presentations. Overall, SSTIs have a higher incidence than urinary tract infections and pneumonia combined and has been steadily rising [1]. Over the past decade, there has been an increase in the incidence of SSTIs presumably due to the aging population, increase in number of immunocompromised people, and the emergence of multi-resistant pathogens [2]. Data from 2012 showed that the total cost of SSTIs in the USA alone was \$13.8 billion, mostly due to hospitalizations [3]. Clearly, cutaneous infections and their management are a significant

health and financial burden and providers should be educated on the most recent developments in order to provide effective, evidence-based care for their patients.

As these infections become more common and complex due to changing epidemiologic and pathogenic characteristics, it is in the benefit of the healthcare provider to be informed on the evolving field of dermatologic infections. Here, we provide a review of the literature on recent updates within the past 5 years on cutaneous infections, focusing on bacterial, viral, and fungal etiologies. The breadth of information and developments on cutaneous infections is vast and so the purpose of this review is to provide succinct, meaningful, and clinically relevant information to the provider for their practice. Within each discussion, we present findings from research on common and significant diseases. Special emphasis is placed on updates to epidemiologic and resistance patterns, treatments, diagnostics, prevention, as well as guidelines.

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Bacteria

Bacterial skin and soft tissue infections (SSTIs) constitute approximately 20% of outpatient dermatology visits and are

among the most common types of bacterial infection [4]. The clinician should be aware of the current treatment recommendations and new antimicrobials that have come to market in order to address the development of multi-drug resistant (MDR) bacteria.

Gram-positive Bacteria

The staphylococcal and streptococcal species are the most common etiologic agents of bacterial SSTIs such as cellulitis and impetigo [4]. Therefore, the majority of updates presented in this section are in regard to these species.

Methicillin-resistant *Staphylococcus aureus*

Most SSTIs are caused by *Staphylococcus aureus*, with 50% of all SSTIs being caused by methicillin-resistant *S. aureus* (MRSA) [5]. Once confined to healthcare facilities, an increase in the development of MRSA has been observed in hospitals, communities, and primary care settings [6]. SSTI antibiotic resistance can mainly be attributed to antibiotic overuse; resistance has been demonstrated with multiple topical antibiotics such as fusidic acid, mupirocin, and retapamulin [6, 7, 8••]. Several studies have shown that there is limited clinical data to support the widespread use of topical antibiotics in preventing infection or promoting wound healing following uncomplicated minor wounds with the exception of impetigo and nasal decolonization of *S. aureus* [8••, 9]. Indeed, a 2015 meta-analysis concluded that nasal mupirocin may have a significant protective effect against MRSA skin infections [10]. The Choosing Wisely Campaign is an American-based educational health campaign which focuses on educating providers and patients on evidence-based medicine, including proper antibiotic use. Providers can access their website for free and look up recommendations and guidelines for antimicrobial use [11].

Several new antibiotics have emerged with efficacy in treating multi-drug SSTIs such as delafloxacin (a fluoroquinolone), omadacycline (an aminomethylcycline), dalbavancin, and oritavancin (lipoglycopeptides) (see Table 1). Delafloxacin and omadacycline were both shown to be non-inferior to linezolid in randomized-controlled trials (RCTs) [17, 23–26]. Other treatment options besides antibiotics have activity against multi-drug resistant (MDR) pathogens as well. Surgihoney Reactive Oxygen (SHRO) therapeutic gel is a safe and cost-effective agent for clearance of wounds from bacteria and biofilms, especially MDR bacteria, as shown by clinical trials [27].

Impetigo

It is estimated that impetigo may affect more than 160 million children worldwide at any given time according to a 2015 report and is most prevalent in tropical and subtropical

resource-poor communities [28]. Topical ozenoxacin was approved for the treatment of impetigo in 2017 (see Table 1). A double-blind RCT demonstrated in patients 2 months and older that 1% ozenoxacin cream was effective and tolerated treatment for impetigo, with 92% of treated patients achieving effective microbiological response after 5 days of therapy [29].

Scalded Skin Syndrome

A case report noted a rapid improvement of scalded skin syndrome in a 71-year-old immunosuppressed patient with the addition of 5000 mg intravenous immune globulin (IVIG) for 3 days in addition to regular antibiotic treatment. Neutralization of toxins via IVIG may be an effective adjuvant treatment for complicated cases [30].

Cellulitis and Erysipelas

A 2019 review reported that the readmission rate of hospital admissions due to cellulitis was 9.8% in 2014 resulting in a cost of \$114.4 million for non-selective readmission attributed to skin infection within 30 days of cellulitis discharge [31]. This can be attributed to misdiagnosis as well as improper treatment and management. Indeed, early consultation of presumed cellulitis with a dermatologist is a cost-effective strategy which improves patient outcomes [32].

Higher patient temperature on admission, higher indicators of inflammation (e.g., C-reactive protein, fibrinogen), lower extremity localization as well as obesity and diabetes were found to be risk factors for erysipelas according to a retrospective analysis [33, 34•]. A prospective hospital-based enrollment study found that early addition of a broader spectrum antibiotic on the second day of treatment in response to suboptimal outcomes on the first day of treatment was not associated with improved outcomes. This suggests that broadening of antibiotic therapy may often be premature, and that an early non-response is not indicative of suboptimal therapy. An RCT demonstrated comparable cure rates for clindamycin and TMP-SMX, however, due to the higher risk of *Clostridioides difficile* infection with clindamycin, TMP-SMX is recommended for oral anti-MRSA coverage of uncomplicated skin infections such as cellulitis and abscesses [35, 36]. Another RCT reported that the use of TMP-SMX and cephalexin did not result in superior clinical results when compared to cephalexin alone for the treatment of uncomplicated cellulitis [37].

Necrotizing Fasciitis

Certain medications can increase the risk of developing necrotizing fasciitis. Non-steroidal anti-inflammatory drugs (NSAIDs) may be associated with development and progression of streptococcal necrotizing infection (although current

Table 1 Summary of recently FDA-approved antimicrobial drugs for skin and subcutaneous infections

Name	Year approved	Indications	Dosing	Adverse effects	Notes
Antibiotics					
Finalexacin (Xtoro™) [12]	2014	Treatment of acute otitis externa caused by susceptible strains of <i>Pseudomonas aeruginosa</i> and <i>Staphylococcus aureus</i>	Four drops of 0.3% solution in affected ear for 7 days	Ear pruritis and nausea	
Delafloxacin (Baxdela™) [13]	2017	Treatment of acute bacterial skin and skin structure infections (ABSSSI) of susceptible species such as gram-positive cocci including <i>Staphylococcus</i> (including MRSA), <i>Streptococcus</i> , and <i>Enterococcus faecalis</i> as well as the Gram-negative species <i>Escherichia coli</i> , <i>Enterobacter cloacae</i> , <i>Klebsiella pneumoniae</i> , and <i>P. aeruginosa</i>	Oral tablet 450 mg every 12 h for 5–14 days Intravenous (IV) 300 mg by infusion over 60 min, every 12 h	Most common include nausea, diarrhea, headache, transaminase elevations, and vomiting Black Box Warning of tendinitis and tendon rupture, peripheral neuropathy, and central nervous system effects	Contraindicated in patients with myasthenia gravis
Ozenoxacin (Xepi™) [14]	2017	Topical treatment of impetigo due to <i>S. aureus</i> or <i>Streptococcus pyogenes</i> in adult and pediatric patients 2 months and older	Apply a thin layer of 1% cream to the affected area twice daily for 5 days	Rosacea and seborrheic dermatitis were reported in one adult patient	
Omadacycline (Nuzyra™) [15]	2018	Treatment of ABSSSI of susceptible species such as gram-positive cocci (including MRSA and <i>E. faecalis</i>), <i>E. cloacae</i> , and <i>K. pneumoniae</i>	Treat for 7–14 days Oral tablet 450 mg once daily on days 1 and 2, then 300 mg once daily IV 200 mg infusion over 60 min OR 100 mg infusion over 30 min twice followed by 100 mg infusion over 30 min once daily OR 300 mg orally once daily	Nausea, vomiting, infusion site reaction, liver enzyme elevations, hypertension, headache, diarrhea, insomnia, and constipation	Contraindicated in second and third trimester of pregnancy as well as children up to age 8
Dalbavancin (Dalvance™) [16]	2014 ^a	Treatment of ABSSSI of susceptible gram-positive cocci including <i>Staphylococcus</i> (including MRSA), <i>Streptococcus</i> , and <i>E. faecalis</i> (vancomycin susceptible strains)	IV: For patients with creatinine clearance (CrCl) \geq 30 mL/min or on hemodialysis, 1500 mg single dose or 1000 mg followed by 500 mg 1 week later. All IV infusions over 30 min For patients with CrCl < 30 mL/min and not on dialysis, reduce above dosages by 25%	Nausea, headache, and diarrhea	Serious hypersensitivity reactions such as anaphylaxis have been reported. Rapid infusion can lead to infusion reactions
Oritavancin (Orbactiv™) [17]	2014	Treatment of adult patients with ABSSSI caused by susceptible gram-positive cocci such as <i>Staphylococcus</i> (including MRSA) and <i>Streptococcus</i> , <i>E. faecalis</i> (vancomycin-susceptible)	IV: 1200 mg single infusion over 3 h	Headache, nausea, vomiting, limb and subcutaneous abscesses, and diarrhea	Shown to artificially elevated PT and PTT. Concomitant use with warfarin may increase risk of bleeding. Hypersensitivity and infusion reactions have been reported
Tedizolid phosphate	2014	Treatment of ABSSSI of susceptible gram-positive cocci including <i>Staphylococcus</i> (including MRSA),	Oral 200 mg once daily for 6 days IV 200 mg infusion once daily for 6 days	Nausea, headache, diarrhea, infusion/injection reaction, vomiting, dizziness	Safety of administration has not been evaluated in neutropenic patients. Tedizolid may increase concentrations

Table 1 (continued)

Name	Year approved	Indications	Dosing	Adverse effects	Notes
(Sivextro®) [18]		<i>Streptococcus</i> , and <i>E. faecalis</i>			of orally administered Breast Cancer Resistance Protein (BCRP) substrates
Antifungals					
Tavaborole (Kerydin™) [19]	2014	Topical treatment of onychomycosis of the toenails due to <i>Trichophyton rubrum</i> or <i>Trichophyton mentagrophytes</i>	Once daily application of 5% topical solution to the toenails for 48 weeks	Application site exfoliation, ingrown toenail, application site erythema, application site dermatitis	Should be applied to entire toenail and under toenail being treated
Eficonazole (Jublia®) [20]	2014	Topical treatment of onychomycosis of the toenails due to <i>T. rubrum</i> or <i>T. mentagrophytes</i>	Once daily application of 10% topical solution to the toenails for 48 weeks	Ingrown toenails, application site dermatitis, application site vesicles, application site pain	Should be applied to entire toenail, toenail folds, toenails beds, hyponychium, and undersurface of toenail plate are covered
Isavuconazonium sulfate (Cresemba®) [21]	2015	Treatment of invasive aspergillosis and invasive mucormycosis in patients 18 years of age and older	Loading dose 372 mg every 8 h for 48 h via oral or IV administration Maintenance dose 372 mg once daily via oral or IV administration starting 12 to 24 h after last loading dose	Most common include: Nausea, vomiting, diarrhea, headache, elevated liver enzymes, hypokalemia, constipation, dyspnea, cough, peripheral edema, and back pain Serious hepatic reactions infusion reactions, and hypersensitivity reactions have been reported	Liver enzymes should be tested at start of and during treatment. Multiple drug-drug interactions. Use in pregnant patients or patients with hepatic impairment should be considered if benefits outweigh risks
Itraconazole capsules (Tolsura™) [22] ^b	2018 ^a	Treatment of pulmonary and extrapulmonary blastomycosis and histoplasmosis, as well as pulmonary and extrapulmonary aspergillosis refractory to amphotericin B	Blastomycosis and histoplasmosis 130 mg to 260 mg daily Aspergillosis 130 mg to 260 mg daily	Most common include nausea, rash, vomiting, edema, headache, diarrhea, fatigue, fever, pruritus, hypertension, abnormal hepatic function, abdominal pain, dizziness, hypokalemia, anorexia, malaise, decreased libido, somnolence, albuminuria, and impotence Serious side effects include hepatotoxicity, cardiac dysrhythmia, peripheral neuropathy, and hearing loss Black box warning of congestive heart failure exacerbation and multiple drug interactions	Not indicated for onychomycosis. Must be administered with food

^a Dosing and administration updated in 2016

^b Itraconazole was initially approved in 1992, however, oral use was approved in 2018

data is conflicting) [38] and the use of sodium-glucose cotransporter 2 inhibitors such as canagliflozin, dapagliflozin, and empagliflozin have been found to be associated with Fournier gangrene [39].

The differential diagnosis for necrotizing fasciitis can include much more benign pathologies based on physical exam alone and so imaging can be a useful technique in order to delineate the depth of tissue involvement. A systematic review concluded that computed tomography (CT) (sensitivity of 88.5% and specificity of 93.3%) is superior to plain radiography (sensitivity of 48.9% and specificity of 94%). The same review concluded the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score was found to have poor sensitivity and thus should not be used to rule out necrotizing soft tissue infection (NSTI) [38].

If there is high suspicion for necrotizing fasciitis, early surgical intervention is crucial. A single academic center experience study reported early surgery within the first 6 h after being diagnosed improves in-hospital outcomes of patients with NSTI [40]. A retrospective study of patients with necrotizing fasciitis and shock associated with Group A *Streptococci* (GAS) or *S. aureus* showed that there was no impact in mortality in patients treated with adjunctive IVIG [41].

Although fungi are uncommonly recovered in polymicrobial necrotizing infection, a study of 230 patients showed that 10.7% of necrotizing fasciitis cultures were positive for fungi. These patients had a three times greater mortality rate and required two more surgical interventions on average compared to patients without fungal infection [42].

Toxic Shock Syndrome

In a study of burn patients with MRSA infection, all with toxic shock syndrome (TSS) had lower TSST-1 antibody levels than those who did not, suggesting that it may be a powerful predictive and preventative clinical tool [43]. IVIG was associated with a significant reduction in 30-day mortality in a 2018 meta-analysis including five studies of patients with streptococcal TSS treated with clindamycin [44].

Actinomyces

Several novel species of *Actinomyces* such as *Actinomyces meyeri* and *Actinomyces neuui* are increasingly being recognized in human infections [45]. The most successful treatment option for actinomycetomas has shown to be trimethoprim-sulfamethoxazole (co-trimoxazole 80/400 to 160/800 mg per day) and amikacin 15 mg/kg per day [46].

Gram-negative Bacteria

Pseudomonas

Data from the National Healthcare Safety Network from 2011 to 2014 showed *Pseudomonas* was the fifth most common cause of surgical site infections (5.7%). In the USA, there has been a trend towards declining rates of resistance though it is still high [47]. The new fluoroquinolones, delafloxacin, and finafloxacin have activity against *Pseudomonas* (see Table 1) [12, 48].

Spirochetes

Syphilis

The manifestations of syphilis are diverse in presentation and severity, with many patients presenting asymptotically and thus highlighting the importance of screening. Although annual syphilis screening advice is recommended for sexually active individuals, a 2015 systematic review suggested the testing of high-risk individuals every 3 months [49, 50••]. The US preventative services task force recommends screening for syphilis in asymptomatic non-pregnant individuals who may have higher risks of infection [50••]. Initial screening with a non-treponemal test is recommended followed by a treponemal test such as the fluorescent treponemal antibody absorption for confirmation [51]. A study of the recently approved rapid fingerstick treponemal-based antibody test called the Syphilis Health Check reported the sensitivity and specificity of the test to be 71.4 and 91.5%, respectively. The ability of both non-medical persons and health care workers to administer the test may position it as a promising diagnostic test of the future [52].

The first-line treatment for syphilis in all phases is typically one intramuscular injection of penicillin G benzathine, however, a 2015 study that demonstrated additional doses of penicillin G benzathine had no effect on treatment response in HIV-infected persons with early syphilis [53]. For patients needing an alternative treatment, a retrospective observational study that showed the combination of 3 g oral amoxicillin and probenecid for a treatment duration of 14 to 30 days was well tolerated and effective for HIV infected males [54].

Mycobacteria

Mycobacteria compose are a large group of ubiquitous microorganisms characterized by acid-fast staining. They can simply be characterized into tuberculous and nontuberculous mycobacteria, the latter of which (specifically *Mycobacteria leprae*) is responsible for Leprosy or Hansen's disease.

Leprosy

Leprosy is exceedingly rare in humans in UK and Europe. Persistent zoonotic transmission of organisms in *M. leprae* complex may occur and preliminary evidence suggests that ticks may be able to ingest *M. leprae* and transfer the organism to their eggs [55, 56]. Overall, the number of patients treated for leprosy has declined steadily over the last three decades, largely in parallel with the shortened duration of treatment with rifampin. The recommendation by the WHO to shorten the duration of treatment from 24 to 12 months was supported by evidence that patients who received only 12 months of treatment responded as favorably as those that received treatment for 24 months [57].

A World Health Organization (WHO) surveillance study evaluating the rate of *M. leprae* antimicrobial resistance between 2009 and 2015 showed resistance to rifampin (3.8%), dapsone (5.3%), and ofloxacin (1.3%) [58]. The WHO 2018 guidelines recommend prophylaxis with single-dose rifampin for those older than 2 years of age [59]. Though single-dose rifampin (SDR) is cheap and simple, there is concern that SDR may lead to increased resistance to rifampin in other bacteria especially *M. tuberculosis* [60]. Several studies are underway to evaluate the benefit of SDR [61]. Routine use of the BCG vaccine and single-dose rifampin either alone or together as preventative tools has been demonstrated as well [62].

Other Nontuberculous Mycobacteria

Several new diagnostic techniques have been developed to identify the various NTM species and subspecies using DNA hybridization as well as sequencing of 16S RNA and other genes [63••]. These include the genotype NT-DR PCR amplification assay (Hain Lifescience, Nehren, Germany) as well as matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry [64, 65]. The genotype NT-DR PCR can detect a variety of NTM species as well as drug resistance to macrolides (79% for clarithromycin) and aminoglycosides (71% sensitivity for amikacin/tobramycin), MALDI-TOF can rapidly differentiate a theoretically unlimited number of species, practically limited by library size, therefore making it a powerful tool in differentiating species with similar genomes such as *M. chimaera* and *M. intracellulare* as reported in one study [65].

Mycobacterial species are notorious for being highly drug resistant and new antimicrobials with activity against NTM have been recently developed. Delamanid (a dihydro-nitroimidazooxazole derivative, not yet US-approved) and tedizolid (an oxazolidinone) both have been shown to have activity against NTM species [63••] (see Table 1).

Tuberculous Mycobacteria

In a study from India, rapid detection via PCR of *M. tuberculosis* in cutaneous tuberculosis had a sensitivity of 25.8% from samples of histopathologically confirmed cutaneous tuberculosis [66]. In another Indian study, the sensitivity of PCR in detecting cutaneous tuberculosis was 24.5%, which was higher than culture (16.3%) [67]. Thus, PCR can be considered an early diagnostic tool for cutaneous tuberculosis especially when acid-fast bacilli staining and culture results are negative or when fresh material has not been collected for culture. A Korean case report described a diagnosis of tuberculosis verrucosa cutis using interferon-gamma release assay (IGRA) with negative culture, staining, and PCR, reflecting the high sensitivity and specificity of IGRA and its utility as a diagnostic tool [68, 69].

Viruses

Viral infections are responsible for some of the most common dermatologic presentations in adults such as oral and genital herpes, warts, and a wide variety of exanthems [70]. Viral infections are classified here based on genetic material and further subdivided into their respective families. Research updates regarding common families such as the herpesviruses and papillomaviruses are described here. Included here are also viral infections that are not considered primarily cutaneous infections, such as Measles and Zika, but do present with cutaneous findings and have been of interest in the medical community as well as the public eye in the recent years.

DNA Viruses

Herpesviridae

The herpesviridae family includes herpes simplex virus (HSV) 1 and 2, varicella-zoster virus, as well as others which can present with distinct cutaneous manifestations and must be managed appropriately. Antivirals in the helicase-primase inhibitor class are on the forefront of pharmacotherapies against alphaherpes viruses [71].

Herpes Labialis A 2017 review concluded that oral antiviral drugs such as acyclovir, valacyclovir, and famciclovir are superior to topical antiviral formulations such as 5% acyclovir ± hydrocortisone, 1% penciclovir, or 50 mg Buccal adhesive tablet for episodic treatment and recurrence. It should be noted that although valacyclovir and famciclovir require less dosing than acyclovir, the former two are not approved for children and are more costly [72]. A 2018 systematic review found that laser treatment with wavelength, power, and energy density ranging from 632.5–870 nm, 5–80 W, and 2.04–48 J/cm² was

consistently effective in reducing healing time and edema of oral herpes lesions. The heterogeneity of the studies warrants further investigation, however [73•].

Herpes Genitalis In 2016, the US Preventive Services Task Force provided a class D recommendation (strongly discouraging use of service) against routine serological screening for HSV in asymptomatic individuals, with a predictive value of HSV02 serologic testing to be 50% [74••].

A 2015 study showed tenofovir gel significantly reduced HSV acquisition in a study of HSV-2 negative women compared to placebo [75]. A separate study showed tenofovir had no significant effect, however, on viral shedding or the number of days with genital lesions in HSV-2 positive women [76].

Neonatal Herpes Neonatal herpes is classified as a TORCH infection which can result in serious consequences for newborns. The American Academy of Pediatrics released new guidelines for neonatal herpes management in 2015 which is briefly summarized here [77].

It was reported that the risk of transmission is greatest (25–60%) among infants delivered vaginally or greater than 4 h after rupture of membranes to mothers with active genital lesions and no history of HSV infection. However, the risk of transmission of HSV to infants born to shedding women due to reactivation of infection during the first half of pregnancy or earlier is relatively low (2%) [77]. Isolation of HSV from surface sites of the neonate obtained greater than 12 to 24 h after birth is considered to always be a significant finding and is the most common and non-invasive method to obtain evidence of active infection with HSV [77]. All neonates born to women with active genital HSV lesions or history of HSV but no active lesions at time of delivery should be monitored for clinical evidence of HSV infection (skin or scalp rashes, conjunctival lesions, irritability, sepsis, etc.) during the first 6 weeks of life [77]. Additionally, women with herpetic breast lesions are advised not to breastfeed from affected breast until resolution of lesion [77]. The CDC advises that the administration of acyclovir be considered for neonates born to women who acquired HSV near term because the risk is high [51].

A 2015 chart review conducted at Seattle Children's Hospital showed that plasma HSV levels have been found to correlate with clinical presentation of neonatal HSV disease and mortality, thus monitoring can be used to help guide the duration of therapy [78].

Varicella-Zoster A zoster recombinant adjuvanted, two-dose subunit vaccine containing recombinant glycoprotein E with novel adjuvant (ASO1b) was approved by the FDA in 2017 and is recommended for immunocompetent adults over 50 [79]. A case report noted that prophylaxis of 10 mg/kg/dose acyclovir prevented varicella infection in children undergoing

chemotherapy in a pediatric oncology ward, suggesting that acyclovir can be a cheap preventative measure in the immunocompromised [80]. An RCT of adults with herpes zoster found that treatment with famciclovir 500 mg three times daily was non-inferior with regard to cure rates compared to acyclovir 800 mg five times a day over the course of 7 days [81].

Papillomaviridae

Human papilloma virus (HPV) causes various wart types such as verruca vulgaris, plantar warts, and condyloma acuminatum as well as a variety of cancers, and several high-risk strains are currently vaccinated against. Quadrivalent human papillomavirus vaccination was shown to be well tolerated and effective for the treatment of recalcitrant cutaneous warts in children, however, large clinical trials are needed [82].

A variety of physical and chemical treatment options for the various presentations of HPV are available. An RCT found that 6% topical hydrogen peroxide served as an effective and safe treatment for non-genital warts compared to 3% hydrogen peroxide or placebo [83]. A 2017 pilot study showed clearance of 75.9% of cutaneous warts with microwave therapy, compared to 23–33% report clearance rate with cryotherapy or sialic acid, indicating microwaves may be a promising treatment for cutaneous warts [84]. Oral isotretinoin (30 mg/day) is also reported to be effective for the treatment of recalcitrant flat facial warts with a manageable safety profile [85].

An RCT of intralesional *Candida albicans* injection showed a high clearance rate (77%) of plantar warts with superior therapeutic outcomes compared to cryotherapy and minimal side effects [86]. Adapalene 0.1% gel resulted in complete clearance of plantar warts in 96% of patients in another study within an average of 37 days without scarring or irritation suggesting another safe and effective treatment option [87]. A phase II study showed efficacy of a novel 2% topical povidone-iodine solution in treating verruca vulgaris with 77% improvement in the Global Aesthetic Improvement Scale, warranting phase III trials [88].

Poxviridae

Clinical trials have shown little to no improvement in treating molluscum contagiosum, caused by poxvirus, with imiquimod in children [9]. A 2017 systematic review did, however, find evidence for salicylic acid, KOH, cantharidin, curettage, and lemon myrtle oil for the treatment of molluscum, all supported by RCTs. The treatment of choice for most patients has shown to be cryotherapy or cantharidin [89]. Molluscum contagiosum will resolve in immunocompetent patients, though, so the clinician should use their discretion when choosing to treat [90].

Polyomaviridae

Merkel Cell Carcinoma Merkel cell polyomavirus (MCPyV) is a nearly-ubiquitous virus which asymptotically infects individuals in early childhood and has been established as the causative agent for the very rare Merkel cell carcinoma [91], 79% of Merkel cell carcinoma biopsies were positive for MCPyV compared to only 12% in control skin samples in a 2015 meta-analysis [92]. One study found that a subset of Meckel cell carcinoma patients (19%) was MCPyV negative and had an increased risk of death compared to those with positive serologies [93]. In another study of 219 patients with Merkel cell carcinoma, 52% were seropositive for antibodies to MCPyV oncoproteins. Seropositivity at the time of diagnosis was found to independently predict decreased disease recurrence. For those who are seropositive, rising antibody titer surveillance may be a useful early indicator of recurrence [94].

Trichodysplasia Spinulosa Trichodysplasia spinulosa is a rare complication of immunosuppressed patients which presents as folliculocentric papules and keratin spicules caused by TS polyomavirus [95]. It has recently been suggested that the clinical manifestations are due to primary infection, rather than reactivation, in immunocompromised patients [96]. Due to its rarity, treatment data on TS is limited. Some reports have mentioned utility in reducing immunosuppression in combination antivirals such as topical cidofovir or oral valganciclovir. BK viremia was used in one case report as a surrogate to measure of over-suppression in order to prevent the complication of graft rejection in a pediatric kidney transplant patient [97]. A 2017 case report also described successful treatment with of TS with leflunomide in an immunosuppressed patient, and may prove a useful agent when conventional therapy has failed [98].

Positive Sense RNA Viruses

Enteroviridae (Coxsackievirus A)

The American Academy of Pediatrics recommends the most important preventative measure of hand-food-and-mouth (HFMD), caused by Coxsackievirus A, is proper hand hygiene, especially when changing diapers as the virus is shed in stool for weeks following symptom presentation [99]. Vaccines for Coxsackie A virus are currently under development [100]. Previously unreported, a 2017 case report identified coxsackievirus A16 as the causative agent of a case of acute pancreatitis in a 3-year-old girl with HFMD, suggesting pancreatitis should be considered in the differential for abdominal pain in patients with HFMD [101].

Togaviridae (Chikungunya Virus)

Chikungunya has rapidly spread over the continental USA over the past 5 years, with most cases associated with travel to Central America. Thus, clinicians should have suspicion of patients in endemic areas and those with relevant travel history who present with arthralgias and a morbilliform rash [102]. A single PCR test was recently developed which tests for chikungunya, dengue, and Zika at once and is available through the CDC and other qualified laboratories [103]. Also, the CDC stated in 2016 that transmission of chikungunya via breast milk has not been reported and that women are encouraged to continue breastfeeding in endemic areas [104]. There can be rare but serious cutaneous manifestations of infection; a 2016 report described three Venezuelan patients with confirmed chikungunya who presented with previously unreported severe nasal skin necrosis early in the course of life-threatening illness where two of the patients eventually died [105].

Negative-sense RNA Viruses

Orthomyxoviridae (Measles Virus)

The recent increase in measles cases has largely been attributed to lack of vaccination, as 71% of cases occurred in undervaccinated individuals and 88% occurred in small undervaccinated communities in 2018 [106]. Preliminary surveillance data from the WHO in April 2019 suggested the incidence of measles had increased by 300% compared to the same time frame in 2018 [106]. Though measles is often classically associated with a rash, multiple cases of acute measles encephalitis without rash have been identified, suggesting that screening for measles virus is necessary in children with viral encephalitis to eliminate the disease [107].

Fungi

The prevalence of fungal infections has been steadily increasing which is in part highly attributable to a growing immunocompromised population as well as an increase in worldwide travel [108]. Fungal infections are divided here into superficial as well as subcutaneous infections, highlighting new pharmacotherapies, guidelines, and prevention.

Superficial Mycoses

The superficial mycoses discussed here include *Malassezia*, dermatophytes, and *Candida*. Superficial fungal infections are quite common as many species are part of the normal skin flora [108].

Malassezia

Malassezia species are responsible for a number of superficial fungal infections such as pityriasis versicolor and *Malassezia* folliculitis [108]. A 2018 study found (1,3)-beta-D-glucan assay may be useful for early identification of invasive yeast infections in neonates and for monitoring antifungal therapy efficacy though it is not effective in setting of invasive *Malassezia* [109].

Predisposing factors to *Malassezia* folliculitis include topical or oral antibiotic use, topical or oral corticosteroid treatment, and immunosuppression [110]. Prohibiting lipid-rich moisturizing hand cream was one of the control measures used that successfully controlled/stopped an outbreak of *Malassezia* in a neonatal intensive care unit [111]. In 2016, the FDA reported that risks of oral ketoconazole outweigh benefits for treatment of *Malassezia* infections, due to risk of liver injury, adrenal gland disorders, and drug interactions [112]. 2015 Danish guidelines reported successful treatment of *Malassezia* folliculitis with isotretinoin and photodynamic therapy [113•].

Dermatophytes

Various diagnostic techniques for dermatophytic infections have recently been developed. MycetColor® and MycetFluo®, which use Congo red and calcofluor dye respectively, are stains which allow for rapid diagnosis of dermatophytes with sensitivities of ~85% [114]. Fluorostaining with Blankophor is able to increase the sensitivity of fluorescence microscopy by 22% in diagnosing dermatophytes compared to light microscopy [115]. If dermatophyte culture is necessary, a 2016 study found that only 17 days of culture growth is necessary to make a positive diagnosis rather than 4 weeks as previously recommended [116]. Taq-Man probe base real-time PCR of the beta-tubulin (BT2) significantly has shown to increase the rate of detection of dermatophytes compared to microscopy, making it a potentially useful diagnostic technique in the clinic [117].

A 2015 systematic review confirmed the efficacy of terbinafine and naftifine in treating *Tinea corporis* and *Tinea cruris* [118]. Additionally, a meta-analysis showed that in children with *Trichophyton* *Tinea capitis* infections, 4 weeks of terbinafine was as effective as 8 weeks of griseofulvin for complete cure [119]. Once-daily luliconazole 1% cream has shown to be effective in treating *tinea pedis*, with strong activity against *Trichophyton* species [120].

Treatment of onychomycosis is necessary as it can significantly affect quality of life and lead to secondary infections, notably in diabetics [121]. Several new therapies for onychomycosis have recently been approved by the FDA. Tavaborole is topical antifungal approved for toenail onychomycosis caused by *Trichophyton rubrum* or *Trichophyton*

mentagrophytes (see Table 1) [19]. Eficonazole was approved for the same indication (see Table 1) [122]. The FDA has also approved laser therapy to temporarily increase the amount of clear nail [123].

Candida

Due to increasing resistance in *Candida* species, physicians should be aware of effective treatment options when encountering patients with infections refractory to first-line treatments. Fluconazole has been shown to be preferred over itraconazole because the latter associated with nausea in more than 10% of patients and is a more potent inhibitor of p450 enzymes [124]. Various treatment alternatives have been shown to be effective in fluconazole-resistant *Candida* such as voriconazole, posaconazole, anidulafungin, an echinocandin, or IV amphotericin B deoxycholate [124, 125]. A newer, extended-release tablet of posaconazole is indicated for the treatment of oropharyngeal candidiasis as well [126].

Subcutaneous and Systemic Mycoses

Subcutaneous and systemic mycoses are typically spread via inoculation into the dermis or via systemic spread. Classic examples of the systemic mycoses include histoplasmosis, blastomycosis, and coccidiomycosis [108]. Isavuconazole is a new FDA-approved azole shown to be tolerated and has clinical activity against endemic dimorphic fungi with a safety profile similar to that observed in large studies (see Table 1) [127, 128].

Mycetoma

In 2016, mycetomas were included in the WHO list of neglected diseases and thus represent a significant health burden in developing countries [129]. The current recommended protocol in endemic areas with meager resources is to start with fine-needle aspiration cytology; if results are negative, the next appropriate step is deep surgical biopsy to obtain grains for culture and conduct histopathological examination [130]. It should be noted that there is a high relapse rate (27%) from surgery in treating eumycetoma according to a study examining patients with *Madurella mycetomatis* [131].

Histoplasmosis

A new capsule formulation of itraconazole (Tolsura™) has shown enhanced bioavailability and was approved for use for histoplasmosis (as well as blastomycosis) in 2018 (see Table 1) [22].

Blastomycosis

Serial urine testing is useful in monitoring disease progression though culture and cytopathology remain the gold standard for diagnosis of blastomycosis [132]. Tolsura™ was also approved for blastomycosis as stated above [22].

Mucormycosis

Approved by the FDA in 2015, isavuconazonium sulfate may be used for the treatment of mucormycosis [133]. In an open-label single-arm study that included 37 patients with proven or probable mucormycosis, IV or oral isavuconazole was similar in efficacy to amphotericin B and was well tolerated [134]. In vitro studies show that posaconazole is also active against mucormycosis and available in parenteral and oral formulations [135].

Coccidioidomycosis

Primary infection with *Coccidioides* has been found to be protective of secondary infections which have led to early investigations of vaccine development [136].

Penicilliosis

For cutaneous form of penicilliosis, itraconazole should be administered, whereas in the case of severe infections, the use of Amphotericin B deoxycholate followed by itraconazole is recommended. Voriconazole may serve as an alternative for both mild and severe cases [137].

Conclusion

In summary, we have presented clinically relevant updates to some of the most common and significant infectious cutaneous diseases within the past 5 years. It is evident that the emergence of resistant strains of microorganisms in all categories described, whether it be bacteria, fungi or viruses, has driven the discovery and production of new antimicrobials which are now at the disposal of the provider. Additionally, new guidelines on treatment as well as prevention strategies are able to aid providers of how to effectively combat this resistance and provide better outcomes for their patients. Advances in diagnostics technology have also become available which can provide an accurate determination of causative agents leading to more directed therapies and potentially reduce the frequency of empiric treatment. Readers should take note of new emerging infections and newly described presentations which they may encounter in their practice. As research advances in this field, new discoveries will continue to change our understanding of basic science as well as clinical management of

cutaneous infections in order to provide the most effective and safe care to patients who will be afflicted by them.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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