Chapter 8
Litigations for Unexpected Adverse Events

8.1 Case 1: Drug-Induced Hepatitis

A 53-year-old Iranian female who immigrated to Canada about 3.5 years before was referred to an internist for a positive Mantoux skin test (11 mm in diameter). The subject was previously well with no symptoms indicative or suggestive of active tuberculosis. A routine tuberculosis skin test was performed because the patient had applied to be a volunteer at a local hospital. She had no significant past illness or known allergies, and she was never diagnosed with nor had known contact with anyone with active tuberculosis. The subject never ingested alcohol and was not known to have hepatitis or be a carrier of any hepatitis virus. Baseline investigations performed by the internist included routine complete blood count, routine biochemical tests (liver enzymes, creatinine, and glucose), serum ferritin, and thyroid-stimulating hormone – all of which were normal. A chest radiograph was reported to be normal.

The patient was prescribed isoniazid 300 mg once daily and pyridoxine 25 mg once daily to be taken for 9 months as treatment for latent tuberculosis. At the follow-up appointment 3 months later, her only symptom was that of knee pain, which was treated as osteoarthritis with diclofenac, a non-steroidal anti-inflammatory drug (NSAID). Five weeks later, she returned to see the internist with a history of increased dark colored urine and yellowish skin discoloration for a few weeks. Blood tests were ordered and patient was referred to a gastroenterologist. She was assessed by the gastroenterologist a week later, who noted symptoms of dark urine and yellowish skin discoloration for a month. The specialist noted the patient to be mildly icteric with a bilirubin of 51 μmol/L (normal <20 μmol/L), the alkaline phosphatase (ALP) was 352 μL (normal 25–96 μL), and the serum glutamate-oxaloacetate transaminase (SGOT) was 1,102 μL (normal 4–28 μL). The isoniazid was then discontinued and further investigations were performed. Serologies for the hepatitis viruses (A, B, and C) revealed no acute infection but immunity to hepatitis A and B, and a liver ultrasound was normal.

The patient’s symptoms over the following week worsened with jaundice, anorexia, malaise, and distention of the abdomen. She was then admitted to a hospital emergency department. Repeat blood tests revealed normal blood count,
creatinine, glucose and electrolytes; but the bilirubin had risen to 219 μmol/L, the SGOT was 978 μL, the serum alanine aminotransferase (ALT) was 641 μL (normal 10–45 μL), ALP 300 μL, and the prothrombin time 2.2 s. A repeat ultrasonography of the abdomen revealed large ascites and a liver of 13 cm in length with normal contour. Over the next 2 weeks, she became drowsy and encephalopathic, and was transferred to a tertiary care hospital where a liver transplantation was successfully performed (live donor from the patient’s daughter). Pathology of the liver showed a markedly shrunken liver with signs of fulminant hepatitis, with negative stains for hepatitis B antigens.

8.1.1 Medico-legal Issues

A lawsuit was subsequently launched by the patient (plaintiff) against the physician who prescribed the isoniazid. The statement of claim alleged the following: (1) isoniazid was directly responsible for the plaintiff’s fulminant hepatitis which resulted in the need for a liver transplant, (2) informed consent was never obtained to prescribe the drug, as the plaintiff was never counseled on the adverse effects, nor given a choice of treatment, (3) use of the isoniazid was never indicated, as the patient had no symptoms or signs of active disease, (4) the physician should have realized that the positive Mantoux test was due to a previous BCG vaccination as a child (the defendant was informed of this fact) and therefore there was no need to treat the plaintiff for latent tuberculosis.

Based on the above facts, the internist was negligent in prescribing isoniazid and he should have monitored her liver enzymes after initiation of treatment (according to the statement of claims). The lawyer for the plaintiff further stipulated that if his client were never treated unnecessarily for latent tuberculosis, she would not have suffered from fulminant hepatitis or required a liver transplant. Hence, the treating physician provided substandard care and compensation was sought for pain and suffering of the plaintiff, as well as for the daughter who underwent partial hepatectomy for liver donation.

8.1.2 Medical Issues

There are several medical issues that need to be addressed here in order to make a valid judgment of the plaintiff’s claims. (1) First, were there medical indications for the use of isoniazid? (2) Did the physician obtain adequate consent for treatment? (3) Can we be sure that the fulminant hepatitis was due to isoniazid? (4) And lastly, could the severe adverse event have been avoided with proper monitoring?

The indications for treatment of latent tuberculosis as recommended by the Center for Disease Control and Prevention (CDC) and the American Thoracic Society are shown in Table 8.1.1.
The case under discussion does not fall into the high-risk category for treatment of latent tuberculosis, but may be considered as an intermediate risk on cursory assessment. Although employees and staff of healthcare facilities, especially those involved in direct patient contact, should be offered treatment of latent tuberculosis, there is no such stipulation for volunteers in hospitals. Most healthcare facilities screen volunteers for active tuberculosis by Mantoux skin test and chest radiograph for those with positive reaction. Another category under which the subject could be considered is an indication for treatment of latent tuberculosis include persons from highly endemic countries within 5 years of immigration with a positive Mantoux test (>10 mm), irrespective of previous BCG vaccination. This group of people represent one of the largest segment of newly diagnosed patients with active tuberculosis in North America and Europe. There are 22 countries with a high burden of tuberculosis (TB) that account for 80% of the TB cases globally. These countries are located predominantly in Asia (South East Asia and Western Pacific regions) Africa, Brazil (South America), the Russian Federation (Eastern Europe), and Afghanistan (Middle East). The estimated new TB cases (all forms) per 100,000 people per year in Iran is 22, which falls in the low risk category (0–24) as present in North America and Western Europe. The incidence and prevalence of TB in the Middle East varies from country to country, and Iran actually falls into the relatively lower risk group.

### Table 8.1 Indications of treatment of latent tuberculosis

| Mantoux reaction (size) | Very high risk |
|-------------------------|----------------|
| HIV/immunosuppression, anti-TNF drugs | ≥5 mm |
| Close contact of active pulmonary TB | ≥5 mm |
| Fibrotic changes on chest x-ray | ≥5 mm |
| Children <5 years old | 0–4 mm |
| Start INH for close contact | |
| Repeat Mantoux in 8–12 weeks, if negative can be stopped. | |
| High risk | |
| Recently infected (≤2 year) | ≥10 mm |
| IVDA/other drug abuse (i.e. crack cocaine) | ≥10 mm |
| High risk conditions (chronic renal failure, diabetes, silicosis, short gut, intestinal bypass, post-gastrectomy, gastric stapling, malnutrition) | ≥10 mm |
| Immigrants from high endemic areas (<5 year) | ≥10 mm (Asia, Africa, Latin America) |
| Residents of long term care (nursing homes, mental institutions, chronic health care) | ≥10 mm |
| Institutions (homeless shelters, correctional facilities) | ≥10 mm |
| Health care workers | ≥10 mm |
| Low risk | Not needed |
of nations. Thus, persons from Iran would not be offered treatment for latent TB based only on country of origin and immigrating to North America within 5 years. The indication for treatment of latent TB in this case is borderline or very debatable, but most physicians (including internists) may not be aware of this fact.

The treatment of choice for latent TB is now standardized to a 9-month course of isoniazid (INH) 300 mg once daily for adults, with or without pyridoxine (vitamin B6) to prevent peripheral neuritis. This is believed to be about 90% effective in preventing future reactivation of TB; but it does not prevent re-infection (with a new strain), which is a risk mainly in highly endemic countries. The main worrisome adverse effect of INH is clinical hepatitis, which can be fatal or lead to fulminant hepatitis that requires liver transplantation. There are two types of hepatic toxicity seen in INH; a common transient elevation of the transaminases seen in 10–30% of patients that occurs within 4–6 months and is benign and asymptomatic, and clinical hepatitis (symptomatic) which is much less common, age-related, and only occurs in about 1% of treated patients. Clinical hepatitis with INH is rare under 20 years of age and increases to about 2–2.3% above 50 years, and in persons >65 years, the risk increases to about 4.5%. About 50% of INH hepatitis occurs in the first few months of treatment and the remainder occurs later up to 12 months (if still on INH). The prognosis of overt INH hepatitis is usually very good if the drugs are discontinued promptly with the first sign of clinical hepatitis. The overall mortality is about 10% or 4.2 per 100,000 patients treated with INH. Middle-aged black women seem to have the worst prognosis from this complication. In the majority of patients, there is clinical and biochemical resolution of signs and laboratory abnormality within 1–2 months of stopping the drug. Occasionally, patients can present or develop a sub-acute, more protracted course that mimics chronic viral hepatitis and leads to cirrhosis.

The pathogenesis of INH hepatotoxicity was initially considered to be an idiosyncratic reaction, but there is increasing evidence that this is a direct toxic effect of metabolite(s). There appears to be a higher risk and greater severity with higher doses, and higher incidence in slow acetylators. Animal experiments show that INH metabolism leads to acetyl hydrazine, which after oxidation forms toxic intermediates. These are thought to produce damaging effects by acetylating or alkylating macromolecules within liver cells, but the exact mechanism of liver cell injury is unknown. In slow acetylators, acetyl hydrazine accumulates and predisposes to hepatotoxicity. Another metabolic pathway involves hydrolysis of INH to hydrazine and isonicotinic acid. Hydrazine is known to be directly hepatotoxic and hydrolysis of INH is increased by alcohol and rifampin. The mechanism of age-related hepatotoxicity is unclear, but could possibly be related to the slowing of acetylation with advancing age.

Most guidelines and recommendations of latent TB strongly discourage treatment with INH in patients with active liver disease. Close clinical and biochemical monitoring for liver toxicity are mainly recommended for subjects with high risk for clinical hepatitis, such as older people (≥65 years), those with history of liver disease, chronic carriers of hepatitis B and C, alcohol abusers, concomitant users of other hepatotoxic drugs, and subjects who suffer from malnutrition or AIDS.
Current textbooks of medicine do not recommend routine biochemical monitoring for healthy adults being treated with INH. In these circumstances, baseline liver tests are performed and patients should be counseled on symptoms of clinical side effects and should be monitored clinically. Some experts and the manufacturer recommend biochemical monitoring for persons >35 years old, pregnant women, (and those within 3 months post-partum), monthly for 3 months, then afterwards at 1–3 month intervals.

INH should be discontinued promptly at the first sign of clinical hepatitis. Symptoms of hepatitis may include fatigue, weakness or fever >3 days, malaise, unexplained anorexia, right upper quadrant pain or discomfort, and jaundice. If the ALT is ≥3–5 times the upper limit of normal, the drug should be discontinued, even if the patient is asymptomatic. Restarting INH at a small dose has been recommended by some experts in asymptomatic patients. It is of interest to note that the American Thoracic Society, the British Thoracic Society, and the Task Force of the European Respiratory Society only recommend regular biochemical monitoring of liver function on multidrug treatment for TB in patients with chronic liver disease or increased serum transaminases prior to treatment. In the case of symptoms of hepatotoxicity, the liver function should be examined. This may be based on the fact that there is no good evidence that routine monitoring of liver function will decrease the chance of fulminant hepatitis or fatality, and prompt discontinuation of medications with first onset of symptoms usually results in full recovery in those with clinical hepatitis.

8.1.3 Hepatitis due to NSAID

The defendants’ lawyer raised a critical question. Is it absolutely certain that the fulminant hepatitis suffered by the patient was due to isoniazid? With any serious adverse event, to make an assessment requires several steps and investigations to reach a valid conclusion. This involves a process of deduction and exclusion of other etiologies (such as hepatitis virus), other agents, and use of Bayes theorem to assess overall probability (definite, probable, or possible), as well as posterior and prior probability (based on known literature reports). Other considerations include temporal relationship with use of the medication, compatibility of clinical features and laboratory data, histopathology data and previous reports, and reproduction of the event by re-challenge with the putative agent. Although this is the most definitive method of proving cause and effect, it is the least used because of the potential risk of harm to the patient and the ethical and moral issues.

The temporal relationship, clinical features, laboratory data, and histology of the liver are all compatible with INH - induced hepatitis. However, the investigation excluded well-known causes of viral hepatitis. The patient was also receiving diclofenac, which started 5 weeks before the clinical diagnosis of hepatitis and 2–3 weeks before the onset of symptoms. Thus, there is a temporal relationship with diclofenac treatment and the onset of clinical hepatitis. NSAIDs in
general are known, but rare causes of drug-induced hepatitis. The incidence of diclofenac-induced clinical hepatitis is about 1–5 per 100,000 users, and the incubation period varies from 3 to 12 weeks (consistent with the present case). Data from the diclofenac monograph (Novartis Pharmaceuticals) indicates that there is a higher incidence of moderate to severe (3–8 times upper limit of normal) and marked (>8 times normal) elevation of transaminases when compared to other NSAIDs. In addition, rare causes of severe hepatic reactions, including liver necrosis, jaundice, and fulminant fatal hepatitis (or requiring liver transplant) have been reported with diclofenac. To date, there is no evidence of enhanced risk of clinical hepatitis in patients receiving both INH and diclofenac or other NSAIDs. Elderly women are more susceptible to NSAIDs-induced hepatitis. Histopathology of the liver usually reveals zone 3 or 5 spotty acute hepatocellular necrosis, but there can be granulomas, cholestasis, hepatic eosinophilia, and even chronic active hepatitis with overuse of NSAIDs. The prognosis is usually very good from withdrawal of NSAIDs. There is no evidence that concurrent treatment with INH and NSAIDs increased the risk or severity of hepatitis.

8.1.4 Summary and Conclusion of Medico-legal Aspects

Treatment for latent TB in the case under discussion was not indicated, but the circumstances could be interpreted as representing a borderline indication to use INH. However, the patient should have been offered the choice of no treatment versus therapy for latent TB. The risk versus benefit should have been discussed and the potential side effects explained to the patient. The patient should have been counseled to discontinue the medication at the first symptoms suggestive of clinical hepatitis.

Monitoring for liver disturbance by biochemical tests is not routinely recommended for patients at low risk for clinical hepatitis, and the physician should not be held responsible for his failure to order these tests. Clinical monitoring however is standard and the physician can be held responsible for either failure to recognize the manifestations of hepatitis, or his failure to promptly withdraw all drugs once these signs appear.

It cannot be concluded that INH was irrefutably culpable for the fulminant hepatitis, but based on the relative risk and incidence, it was more likely the cause than diclofenac. In any case, both drugs should have been discontinued immediately with the first signs of clinical hepatitis.

8.2 Case 2: Severe Drug Rash

For 2 years, a 35-year-old male had suffered from recurrent bouts of nasal congestion, nasal discharge, and post-nasal drip with only partial, temporary relief from decongestants, antihistamines, and topical corticosteroids. His FP referred him to an internist and clinical allergist for further management. His past history
was negative for any significant medical illness, but the patient had previous surgery for nasal septal deviation, and had stopped smoking 2 years before.

Examination by the allergist revealed inflamed edematous nasal mucosa with some purulent discharge, and a radiograph of the sinuses demonstrated mucosal thickening of both maxillary antra. Based on these findings, the consultant made a diagnosis of chronic rhino-sinusitis with an allergic and infectious component. The consultant prescribed intranasal corticosteroids and a 2-week course of trimethoprim-sulfamethoxazole (TMP-SMX). The patient reported that he was treated by his FP 2 months before with triple sulfonamide antibiotics (trisulpham) for 7 days without any side effects. He had no known drug allergies before this visit.

Towards the end of the 2-week course of TMP-SMX, the patient developed malaise, low-grade fever, and a body rash that started on the face and trunk. This rash rapidly progressed over the next 48 h to involve his limbs, mouth, and eyes, with blistering of the skin. He was admitted to the emergency department of a hospital with a diagnosis of sulfonamide-induced toxic epidermal necrolysis (TEN). Further care was performed in the burn unit. As a consequence of this adverse reaction, the patient developed bilateral corneal ulcerations requiring repeated corneal transplants. Despite this, he remained blind in the left eye and had severe visual impairment on the right side.

8.2.1 Medico-legal Issues

Medico-legal actions were launched by the patient’s lawyer claiming medical malpractice against the allergist in failing to warn the patient of the potential adverse effects of TMP-SMX. Moreover, the plaintiff claimed that antibiotics were never needed in the first place and if he had known of these potential side effects, he would not have agreed to be treated with the TMP-SMX.

The defense retorted that the adverse reaction suffered by the patient was extremely rare, and that the patient had previously been treated with sulfonamides, without any reaction. They claimed this reaction could not have been predicted and that it was not the standard medical practice for physicians to list all the rare side effects of licensed drugs on the market.

8.2.2 Medical Issues

The first relevant issue in this case is the following question: Should any antibiotic have been prescribed? If antibiotics were indicated, was the choice of the TMP-SMX appropriate? Current consensus is that antibiotics are overused and prescribed unnecessarily for sinus disease.

Sinusitis is commonly due to respiratory viruses and allergic reaction (as in hay fever), and antibiotics are of no value in these situations. The presence of purulent
nasal discharge can be seen in the above conditions, but is not diagnostic or indicative of bacterial sinusitis.\textsuperscript{13} Radiographs of sinuses showing thickened mucosa or fluid in the chambers are non-specific and not diagnostic of bacterial sinusitis, as these changes can also be seen in viral infection and allergic sinusitis.

The etiology of chronic sinusitis is complex and there is a lack of consensus of the pathogenesis. Multiple factors may predispose to chronic sinusitis and allergy appears to play a prominent role, with or without polyps.\textsuperscript{13} Other factors include structural abnormalities (outflow obstruction, retention cysts, etc.) and irritants such as smoking. Chronic sinusitis is usually defined as having symptoms of sinus inflammation lasting longer than 12 weeks, with documented inflammation (by imaging techniques) at least 4 weeks after appropriate therapy with no intervening acute infection.\textsuperscript{14} Computerized tomography (CT) is the preferred imaging technique to identify any obstruction and polyps. Although antibiotics are commonly used in chronic sinusitis, their benefits have not been established by randomized trials, and the role of bacterial superinfection has not been well-defined.\textsuperscript{13} The best microbiological data from patients with chronic sinusitis have found aerobic (52.2\%) and anaerobic pathogens (47.8\%) are common in these cases.\textsuperscript{15} The most common aerobes were \textit{Streptococcus} species and \textit{Hemophilus influenzae} (non-typable strains), and the most common anaerobes were \textit{Prevotella} species, anaerobic \textit{Streptococci} and \textit{Fusobacterium} species.

Management of chronic sinusitis is challenging and involves combined medical and surgical therapy. For surgical cases where there is good clinical and imaging evidence of chronic bacterial sinusitis, empiric antibiotics should be effective against \textit{Streptococci}, \textit{H. influenzae} and anaerobes. Amoxicillin-clavulanate would be a suitable choice, and for β-lactam allergic patients, a new fluoroquinolone with anaerobic activity (moxifloxacin) would be an acceptable alternative.\textsuperscript{13} Failure to respond usually indicates the need for surgery which can be performed by endoscopy, and in these cases, antibiotic treatment should be guided by sinus culture (by puncture or endoscopy-guided). Although antimicrobials are commonly used for extended periods (3–4 weeks) for acute superinfection or exacerbation, no studies have addressed the issue of duration of therapy.

Although the case under discussion may not meet the diagnostic criteria for chronic bacterial sinusitis, making this diagnosis and instituting antibiotic therapy (although a judgment error) should not be considered gross negligence, or represent substandard care to merit malpractice litigation. The choice of antibiotic (even if the diagnosis of chronic sinusitis were correct), however, would not be a suitable selection. For acute bacterial sinusitis, amoxicillin/ampicillin is considered the drug of choice and TMP-SMX is recommended as an alternative agent for subjects allergic to penicillin.

What counseling should patients receive when prescribing an antibiotic, and specifically TMP-SMX? Most physicians do not spend time to inform their patients about the adverse effects of prescribed medications. On the other hand, most pharmacists do provide written information on new prescriptions. Physicians cannot depend on this fact though, nor rely on this service for defense in a court of law. In most situations, physicians may counsel patients on drugs with known high risk
of toxicity or side effects. For frequently prescribed medications (such as most oral antibiotics), counseling often is neglected, or only the common adverse effects are mentioned.

The incidence of uncomplicated skin reaction (allergic skin rash) to TMP-SMX (mainly due to the sulfonamide component) in the general population is about 1–4% of recipients.\textsuperscript{16} This consists of mainly toxic erythema, a maculopapular eruption, infrequently urticaria, erythema nodosum, and fixed drug eruption.\textsuperscript{16} Severe skin reactions in TMP-SMX recipients are rare and include Steven’s-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), exfoliative dermatitis, and necrotizing cutaneous vasculitis. Previous estimates of severe skin reaction were 1 in 100,000 recipients.\textsuperscript{16} Patients with HIV infection have a much higher incidence of cutaneous reaction to TMP-SMX (especially those with AIDS).

### 8.2.3 Epidermal Necrolysis

Epidermal necrolysis (EN) is a rare and life-threatening reaction, mainly drug induced, which encompasses SJS and TEN. These two conditions represent severity variants of identical process and differ only in the percentage of body surface involved.\textsuperscript{17} The incidence of SJS and TEN are estimated at 1.6 per million person-years and 0.4–1.2 cases per million person-years, respectively.\textsuperscript{17} Although EN can occur at any age, it increases in prevalence after the fourth decade, and is more frequent in women. There is some evidence that the risk of EN increases with HIV, collagen vascular disorders, and cancers.

The clinical features of EN are characterized by skin and mucous membrane involvement. Initially, the skin reaction begins with macules (mainly localized to the trunk, face, and proximal limbs), and then progresses to involve the rest of the body and become confluent with flaccid blisters leading to epidermal detachment.\textsuperscript{17} Patients may become systematically ill with fever, dehydration, hypovolemia, secondary bacterial infection, esophageal and pulmonary involvement, and complications and death from sepsis.

The pathogenesis of EN is not completely understood, but studies indicate cell mediated cytotoxic reaction against keratinocytes leading to massive apoptosis. Early in the process, there is a predominance of CD\textsubscript{8} killer T lymphocytes in the epidermis and dermis of bullous lesions, and later monocytes develop. Cytotoxic CD\textsubscript{8} T cells express \( \alpha–\beta \) T cell receptors are able to kill cells through production of perforin and granzyme B. Drugs are the most important causes of EN and TEN and >100 different drugs are implicated. CD\textsubscript{8} oligoclonal expansion corresponds to a drug specific, major histocompatibility complex (MHC) – restricted cytotoxicity against keratinocytes.\textsuperscript{17} Pro-inflammatory cytokines IL-6, TNF\( \alpha \), and Fas ligand are also present in skin lesions. Genetic susceptibility appears to be important, and there is strong association with Han Chinese with HLA-B5802 leucocyte antigen and SJS induced by carbamazepine, and HLA-B5801 antigen and SJS induced by allopurinol.\textsuperscript{17}
High-risk drugs (about 12) from six different classes, account for 50% of EN reactions. These include allopurinol, sulfonamides, anticonvulsants (carbamazepine, phenobarbital, lamotrigine), nevirapine (non-nucleoside analog), oxicam NSAIDS, and thiacetazone. The incubation period for EN ranges from 4 to 30 days, but most cases occur within 8 weeks of starting the medication. Rare cases can appear within hours of use, or same day if they had prior reaction. Early, non-specific symptoms (fever, headache, rhinitis, myalgias) may precede mucocutaneous lesions by 1–3 days. Some patients may also present with pain on swallowing or stinging of the eyes. About one third of patients begin with non-specific symptoms, another third with primary mucous membrane involvement, and the rest present with an exanthema. Progression from a localized area to full body involvement can vary from hours to days. The classification of EN depends on areas of detachable epidermis by a positive Nikolsky sign (dislodgement of epidermis by lateral pressure) and flaccid blisters. The diagnosis of SJS is made when there is less than 10% body surface area (BSA) involvement; SJS/TEN overlaps with 10–30% BSA, and TEN for >30% BSA involvement. In severe cases of EN, the mucous membranes (buccal, ocular, genital) are involved in about 90%, and 85% have conjunctival affliction consisting mainly of hyperemia, erosions, chemosis, photophobia, and excessive lacrimation. Severe form of eye involvement can result in shedding of eyelashes, corneal ulceration (as in Case 2), anterior uveitis, and purulent conjunctivitis.

Extra-cutaneous complications mainly seen in severe TEN may include pulmonary disease (25%) with hypoxia, hemoptysis, bronchial mucosal casts, interstitial changes, and acute respiratory distress syndrome (ARDS), which carries a poor prognosis. The gastrointestinal tract involvement is less common, but can include esophageal necrosis, small bowel disease with malabsorption, and colonic disease (diffuse diarrhea and bleeding). Renal involvement is mainly proteinuria and hematuria, but proximal renal tubular damage can sometimes cause renal failure.

Late ophthalmic complications occur in about 20–75% and consist of abnormal lacrimation with dry eyes, trichiasis (ingrowing eyelashes), entropion (inversion of eyelid), and visual impairment or blindness from scarring of the cornea.

Prognosis of EN varies with the severity of illness and prompt withdrawal of the offending agent. The overall mortality of EN is 20–25%, but for SJS it is lower, at 5–12%, and higher for TEN >30%. Development of a prognostic scoring system (SCORTEN) for TEN, has recently been found useful, but the performance of the score in prediction is best on day 3 of hospitalization. The prognostic factors that are each given one point include the following: age >40 years, heart rate >120/min, cancer, or hematologic malignancy, BSA involved >10%, serum bicarbonate <20 mM/L, and serum glucose >14 mM/L. The mortality rate in TEN increases with accumulation of points as follows: 0–1 point has a mortality rate of 3.2%, 2 points has a mortality rate of 12.1%, 3 points has a mortality rate of 35.8%, 4 points result in a mortality rate of 58.3%, and >5 points result in nearly uniform mortality of 90%.

Management of EN or TEN consists of prompt removal of the offending agent and symptomatic therapy. Patients with a SCORTEN of 0–1 can be managed on the
regular medical wards, whereas those with > 2 points should be transferred to a burn center or intensive care unit (ICU).\textsuperscript{17} It is most important to maintain hemodynamic support with adequate fluids and electrolyte balance. Central venous lines should be avoided because the risk of superinfection is high, and so peripheral intravenous access should be used. Moreover, the rash and blistering is greatest proximally. Nutritional support should be maintained orally or by nasogastric tube, and use of prophylactic heparin is warranted, and also an air-fluidized mattress preferable. Unlike severe burns, extensive and aggressive debridement of necrotic epidermis is not recommended.\textsuperscript{17} There is no indication for prophylactic antibiotics, but patients should be monitored diligently for infection and treated promptly when present. There is no standard protocol for skin dressing, and antiseptic is used depending on the individualized center’s experience. Eye care should consist of a daily examination, artificial tears, antiseptic and vitamin A drops every 2 h. Regular mouth rinse with antiseptic solution several times a day is recommended.

There is no proven specific therapy for any form of EN. Steroids were initially considered for SJS, but their value is unproven, controversial, and they are not routinely recommended. Intravenous immunoglobulin (IVIG) is also very controversial, and although initial retrospective studies suggested benefit, recent prospective, non-randomized studies have not confirmed any definite value, and some studies showed increased renal failure and mortality with IVIG.\textsuperscript{21} In one of the largest studies from a single center, IVIG was assessed in a prospective non-comparative study of 34 patients with EN, and 20 subjects with TEN. There was no evidence of improvement in mortality, progression of detachment, nor re-epidermalization. Most deaths occurred in elderly patients with initially impaired renal function. Thus, IVIG is not recommended for EN unless being assessed in a randomized clinical trial. The death rate with IVIG was 32%, which was higher than the historical death rate in the same center (20%), in historical controls with TEN not treated with IVIG.\textsuperscript{22} Thus, IVIG may be harmful in patients with EN.

8.2.4 Discussion of Medico-legal Issues

One of the issues raised by the plaintiff was that he was not counseled on the potential severe side effects of the TMP-SMX, and that if he were aware of the risk, he would not have agreed to take it. Is it the responsibility of the physicians to explain all potential albeit rare adverse effects of any treatment? The courts may take in consideration the standard practice of the physician’s peers, or what is considered accepted practice. Most physicians (if they do counsel patients on medications) would mention the most common side effects, but would not usually mention rare adverse effects. For instance, it would be justifiable to mention that a drug rash could be seen with TMP-SMX, if the patient happens to be allergic to the drug (which should be discontinued as soon as this occurs). As physicians, we would not usually mention that there is a rare risk of shedding of the skin, blindness, or death. Similarly, when prescribing penicillin in patients not known allergic to the
drug, we generally do not counsel that there is a 1:50,000 to 1:300,000 risk of dying from anaphylaxis (which is treatable). Yet, if we were to order or prescribe chloramphenicol, it is expected that we should counsel the patient that there is a 1:50,000 to 1:300,000 risk of aplastic anemia, which is not treatable except by bone marrow transplantation. Hence, it may be asked; what is the best method of informing patients on medication toxicity? It is acceptable to leave this to pharmacists to provide literature on these drugs as the sole form of counseling. It is the prescriber’s responsibility to obtain informed consent before ordering the medications.

It may be the best policy for prescribers to list the most common side effects, then occasional severe adverse reactions, and mention a possibility of other rare unforeseen adverse reaction (without specifying these latter reactions unless requested by the patient). The details of the counseling may vary on several factors, such as the relative safety profile (therapeutic to toxic ratio), enhanced risk factor for side effects (which may depend on underlying comorbidities or genetic predisposition), and the expected duration of treatment; as the longer an individual is exposed to a drug, the greater the potential for some side effects.

The CMPA have provided some guidelines for risk management considerations in prescribing opioids that are useful for all medication orders and may curtail medico-legal cases from drug adverse events. These medico-legal considerations are:

1. Is there an appropriate indication for this drug?
2. Is the starting dose and need for continuation appropriate?
3. Have you considered the need for monitoring that would be reasonable for your patient?
4. Have you considered the potential effect of any concomitant medication that might influence the dosing, monitoring, and side effects?
5. Have you considered other factors such as comorbidity that might influence the dosing and monitoring?
6. Are you prepared to diagnose and manage any adverse event?
7. Have you counseled the patient on potential side effects, how to recognize early signs, and necessary actions?
8. When discharging patients, have you provided reasonable information about the risks of adverse reactions, precautions to be observed, and person to notify?

Patients who suffer from adverse effects may be willing to forgive a physician’s failure to provide informed consent when that therapy is indicated. However, in situations where the treatments were not indicated, or of questionable value, then any adverse event would likely be unacceptable to the plaintiff or courts.

8.3 Case 3: Failure to Recognize Complications of Steroid

A 38-year-old male with steroid-dependent Crohn’s colitis (diagnosed 6 years before) called his FP for advice regarding chickenpox from his young son who was recently diagnosed with it at a daycare center. The patient was experiencing
retrosternal and epigastric pain on swallowing. The FP prescribed omeprazole 20 mg once daily and ibuprofen over the phone, without seeing the patient. Later in the night of the same day, the man presented to the emergency department of a local hospital. The ER physician noted that the patient was chronically on methylprednisolone 8 mg once daily for Crohn’s disease, and that he had developed local pustules consistent with early varicella within the past 4 days. However, the main concern of the patient was severe retrosternal, mid-chest pain on swallowing and radiating through his back for 24 h. The recorded vital signs showed a temperature of 38.3°C, blood pressure of 155/110 mmHg, heart rate of 81/min, and respiratory rate of 20/min. The examination revealed scattered vesicles/pustules on the patient’s face, soft palate, and pharynx. Treatment on discharge consisted of liquid bupivacaine swish and swallow (topical anesthetic), oxycodone-acetaminophen, and metoclopramide. An electrocardiogram was normal and the discharge diagnosis listed possible esophageal involvement with varicella.

Within 72 h, the subject returned to the same ER with worsening symptoms, and was seen by the same physician. The symptoms consisted of swelling of his face, fever, sweats, productive cough of blood-streaked sputum, and persistent chest pain. Examination reports revealed a very ill looking male with a temperature of 39.5°C, heart rate of 169/min, blood pressure of 131/87 mmHg, and respiratory rate of 30/min. His face was swollen and edematous with closure of the right eye, extensive vesicles and pustules on the face, soft palate with edema and inflammation of the gingivae, and numerous skin lesions over the trunk and proximal limbs. Oxygen saturation on room air was 92% and the chest radiograph was reported as normal.

Investigations revealed anemia, thrombocytopenia, liver disturbance, and evidence of disseminated intravascular coagulopathy. Intravenous acyclovir was started and the patient was transferred to the ICU of a tertiary care center, where he died within 38 h after the second presentation. Autopsy revealed disseminated varicella with involvement of the brain, lung, heart, liver, esophagus, and stomach.

### 8.3.1 Medico-legal Issues

The wife and family of the deceased man launched medical malpractice litigation against the FP, ER attending physician, and the local hospital. Charges against the FP were as follows: (1) substandard care reasonably expected of a general practitioner, (2) he should have advised or warned the patient and provided early treatment, especially since he knew that his son had chickenpox, (3) he knew, or ought to have known that the deceased was immunosuppressed from chronic steroids and therefore at increased risk, (4) he failed to provide medical assistance and prescribe the correct drug (acyclovir) on presentation, (5) he failed to make the patient aware of the potential complications of his long-term steroid use, and (6) he failed to refer the deceased to an appropriate specialist.
The accusations against the ER attending physician were similar: (1) his negligence was the direct cause of the deceased’s death, (2) his medical care fell below the standard reasonably expected from an ER physician, (3) he ought to have known that the patient was immunosuppressed from steroids, and therefore at high risk for complications from chickenpox, (4) he failed to provide proper medical assistance and treatment, (5) he failed to appropriately admit the patient on initial presentation and institute intravenous acyclovir, and (6) he failed to consult an appropriate specialist (internist or infectious disease specialist).

Damages were sought by the plaintiffs for pain and suffering, deprivation of a husband and father, loss of economic benefit afforded to the family from potential employment earnings of the deceased over the next 27 years (assuming retirement at age 65).

Counsel for the defendants requested expert opinion on two key issues: (1) was the steroid dose the deceased received sufficient to cause immunosuppression? (2) If appropriate therapy with acyclovir were started at initial presentation with chickenpox, would the outcome have been any different?

### 8.3.2 Medical Aspects of Chickenpox and Immunosuppression

Chickenpox (varicella) has dramatically declined in all age groups, but most markedly in children since the introduction of varicella vaccine in 1995 in North America and developed countries. Since the introduction of the vaccine, the decline in varicella-related hospitalization in the US was greatest among 0–4 year-old children, but rates also declined in older youths (5–19 year) and adults. In temperate regions, 90% of cases of varicella occur in children <10 years of age, 5% occur in individuals >15 years old, and adults (>20 year) only account for 2%. The risk of hospitalization and death is greater in young infants and adults than children, and most varicella-related deaths occur in previously healthy people. Although varicella is much less common in adults than children, 47% of the deaths from complications occur in adults. In tropical and subtropical countries, the mean age of patients with varicella is higher than in temperate regions, and up to 40% of immigrants from these areas are susceptible to varicella.

Healthy children rarely suffer from complications of varicella, with the most common one being secondary bacterial infection (*Streptococcus* and *Staphylococcus*) of the skin and soft tissue. Immunocompromised children are predisposed to more severe and progressive diseases (up to one third) with multiple organ involvement, lungs, liver, and central nervous system issues being the most frequent. Mortality in these children range from 15% to 18% and those with lympho-proliferative malignancies on chemotherapy have the greatest risk.

Bone marrow transplant recipients also have a high risk of varicella zoster virus (VZV) infection, with a probability of VZV infection at 30% by 1 year after transplant. In a series of 231 cases of VZV infection, 36 presented with chickenpox and 195 with herpes zoster. The overall VZV infection mortality was
High dose corticosteroids are also associated with significant complications of varicella and herpes zoster.\textsuperscript{29} Immunosuppression is most commonly seen with high daily dose of $\geq 1$ mg/kg of prednisone or moderate doses for prolonged periods. Rates of infectious complication were not increased in patients given a daily dose of less than 10 mg daily, or a cumulative dose of less than 700 mg prednisone in a meta-analysis of 73 controlled trials.\textsuperscript{30} Many experts consider prolonged daily dose $\geq 15$ mg prednisone or equivalent to be immunosuppressive. The US Food and Drug Administration (FDA) states that low doses of prednisone (or similar agents) for prolonged periods may also increase the risk of infection.\textsuperscript{31}

Corticosteroids can suppress several stages of the immune response that leads to inflammation, but the main immunosuppressive effect is on the cellular immunity. Thus, steroids can increase the risk and severity of a variety of infectious agents (virus, bacteria, fungi, and parasites). Most notable are agents that require intact cellular immunity for control and eradication, such as herpes viruses, mycobacteria, listeria, nocardia, pneumocystis, candida, cryptococci, toxoplasma, and strongyloides, etc., are increased in patients on prolonged corticosteroids.

The effect of corticosteroids on the inflammatory and immune responses is pleomorphic. An earlier study in guinea pigs demonstrated that similar levels of lymphocytopenia were induced by acute and chronic corticosteroid administration, but only chronic treatment was associated with depression of certain cell-mediated lymphocyte functions.\textsuperscript{32} Chronic cortisone treatment resulted in marked decrease in both antigen-induced migration inhibitory factor (MIF) and proliferation, although mitogen responses remained normal. Over the last few decades, corticosteroids have been found to inhibit the function of various cell types: (1) macrophage/monocytes – inhibit cyclooxygenase-2 and phospholipase A\textsubscript{2} (interrupting prostaglandin and leukotriene pathways), and suppress cytokine production and release of interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-\textgreek{z}, (2) endothelial cells – impair endothelial leukocyte adhesion molecule-I (ELAM-I), and intracellular adhesion molecule-I (ICAM-I), that are critical for leucocyte localization, (3) basophils – block histamine and leukotriene 4c IgE-dependent release, (4) fibroblast – inhibit arachidonic pathway (as with monocytes) and suppress growth factor-induced DNA synthesis and fibroblast proliferation, (5) lymphocytes – inhibit cytokines IL-1, IL-2, IL-3, IL-6, TNF-\textgreek{z}, GM-CSF, and interferon \textgreek{g} production or expression.\textsuperscript{33}

The association of steroid therapy and increased risk, severity and complications of VZV infections has been well established for decades.\textsuperscript{34} Patients receiving high-dose corticosteroids are at risk for disseminated disease and fatality, whereas patients on low-dose schedules are not at increased risk.\textsuperscript{34,35} Esophagitis and gastrointestinal involvement of VZV are distinctly rare and have been described in both immunocompromised hosts and apparently healthy subjects as complications of chickenpox or herpes zoster. Disseminated varicella in autopsy studies of children with acute lymphoblastic leukemia or lymphoma on chemotherapy had demonstrated involvement of the esophagus, small bowel, colon, liver, spleen, and
pancreas. Rare cases of adult varicella on chronic steroids (for asthma) have been reported with small bowel involvement presenting with abdominal pain and gastrointestinal bleeding. However, it appears that the patient may have been on moderately high dose of methylprednisolone (40 mg daily). In an immunocompetent young adult on inhaled steroids for asthma, varicella has been reported to cause diffuse abdominal pain and tenderness with hepatic, esophageal, and pulmonary involvement, with recovery after acyclovir therapy.

Bullous and necrotic ulcerative lesions of the esophagus and stomach have been described in the pathology literature of fatal varicella as early as 1940. Stomach and small bowel changes detected by radiological imaging has also been reported in a case of chickenpox. Occasionally healthy adults with varicella may have mild symptoms of esophagitis that respond to antihistamine-H2 blockers, suggesting temporary esophageal reflux. Shingles esophagitis have also been seen on endoscopy in patients without widespread dissemination of herpes zoster and benign course.

8.3.3 Discussion of Medico-legal Aspects

The deceased patient (Case 3) was receiving 8 mg daily of methylprednisolone prior to his presentation with chickenpox. This dose is equivalent to 10 mg prednisone and normally would not be considered to be immunosuppressive. However, the course of the disease and widespread dissemination with fatality resembles that of an immunocompromised host. How can we explain this reaction? The possibilities include: (1) inaccurate history of the steroid dose provided by the patient, (2) rarely, dissemination and fatality can occur in healthy adults, (3) unrecognized immunocompromised state such as HIV infection or rare genetic mutations, or polymorphisms in genes involved in cellular immunity, and (4) higher free active concentration of the drug than would be expected. Methylprednisolone (Medrol) is 70% bound to protein, mainly albumin, and decrease in serum albumin by 30–50% could increase the active unbound drug almost to the same proportion. On admission to hospital, the patient’s serum albumin was 15 g/L (lower limit of normal 35 g/L), 42% of the normal lower limit. Although the serum albumin can decrease in acute illness from varicella, the half-life of circulating albumin is 15 days and thus, even after 7 days of chickenpox, it should not decrease more than 25% below normal, even if his liver stopped producing any protein (which is not likely). Hence, the patient probably had a chronically low serum albumin from his chronic colitis. His free concentration of corticosteroid should have been greater than 50% of his expected active drug, which is equivalent to ≥15 mg prednisone/day.

Can this information absolve the defendants from responsibility of the patient’s adverse outcome? It could be argued by the defendants that it is not common knowledge or usual practice to consider the protein binding effects of drugs on
their toxicity. Furthermore, it would not be expected that the FP and ER physicians be cognizant of these facts. The defendants maintain that their management did not fall below the expected standard of care, and most reasonable physicians would not have considered the patient immunocompromised on such a low dose of prednisolone. The outcome was unpredictable and only in hindsight was it evident that the deceased was likely immunocompromised and susceptible to a higher risk for adverse outcome.

Experts’ opinions for the plaintiffs’ side argued that the involved physicians should have been aware that adults (even normal hosts) are at a greater risk of severe disease and complications than children from chickenpox are. Therefore, the FP and ER physician were remiss in not prescribing antiviral drug (acyclovir). The ER physician should have admitted the deceased at the first presentation and started intravenous acyclovir, as he suspected visceral dissemination (esophagitis) with varicella, irrespective of the immune state of the patient.

Previous randomized control trial (RCT) of oral acyclovir therapy for uncomplicated varicella in healthy adults have reported mild clinical benefit (decrease of symptoms, fever and time to cutaneous healing), but only in those initiating treatment within 24 h of the rash. Late treatment (25–72 h) had no benefit. The low frequency of serious complications (pneumonia, encephalitis, or death) precluded any evaluation of acyclovir on these outcomes. In immunocompromised patients with VZV infection, later initiation of therapy (≥72 h after onset of rash) may be of value. Although there is no RCT to prove the benefit of intravenous acyclovir in normal adults with varicella complicated by visceral involvement, observational and cohort studies suggest benefit. Thus, intravenous acyclovir continues to be the standard therapy for healthy adults and immunocompromised hosts with clinically significant visceral disease (pneumonia, encephalitis) or dissemination.

8.4 Precautions for Chronic Steroid Therapy

Chronic corticosteroid therapy can have numerous side effects and complications. It is important for physicians to counsel their patients on these potential adverse events, and provide a risk-benefit assessment. Many organs and systems in the body can be adversely affected by chronic steroid therapy (endocrine, bone, eyes, muscle, brain, immune system, skin, etc.). It is important to counsel on potential increased risk of infectious diseases and certain precautions should be taken before embarking on chronic therapy. These include a Mantoux skin test and treatment for latent tuberculosis in those with positive reactions and about to receive prednisone ≥15 mg/day for ≥30 days. A baseline chest radiograph for active or inactive disease should be performed beforehand. It is also recommended that steroid dependent children should undergo VZV antibody test, and if this were negative, then varicella vaccination should be offered. It seems prudent to apply these guidelines to adults as well on chronic steroid therapy. For patients with previous
chickenpox or adequate antibodies, varicella zoster vaccine may be considered to reduce the risk and severity of shingles. This vaccine, a live attenuated vaccine has been found effective and is recommended for persons ≥60 years of age to reduce the burden of illness and incidence of postherpetic neuralgia. Presently, this vaccine is not indicated in immunocompromised adults, so it should be administered before starting prolonged steroids. The product monograph of Zostavax™ (Merck), states that the varicella zoster vaccine is contraindicated in patients receiving high-dose corticosteroid, but not contraindicated for individuals on inhaled or low-dose steroids. The varicella vaccine has been found safe in children with moderate immune deficiency, but it is contraindicated in those with substantial suppression of cellular immunity (as with high-dose steroid).

What should have been the appropriate steps of action in this case? Once the FP was notified that the patient’s child had chickenpox, he should have counseled the father and determined his previous past history or antibody level against VZV. For patients considered non-immune and severely immunosuppressed (moderate to high-dose corticosteroid (≥20 mg/day) VZV immune globulin should be offered and treatment with acyclovir should be instituted at the first sign of varicella. Since the deceased was considered to be receiving a low dose of steroid, then it was more appropriate to offer treatment with acyclovir at the first sign of a typical rash, or provide a prescription to be filled within 24 h of onset of varicella.

References

1. McEvoy GK, Miller J, Kesler L, Welsch OH (eds), (2009). Isoniazid. In: AHFS Drug Information. Am Soc Health Syst Pharmacists, Bethesda, p. 580–585.
2. Geng E, Kreiswirth B, Driver C, Li J, Burzynski J, Della Latta P, La Pas A, Schluger NW, (2002). Changes in the transmission of tuberculosis in the New York City from 1990 to 1999. N Engl J Med 346:1453–1458.
3. Martinez-Lirola M, Alonso-Rodriguez N, Sanchez ML, Herranz M, Andries S, Penafiel T, Rogado ML, Cabezuelas T, Martinez J, Lucerna MA, Rodriguez M, Bonillo MDC, Bouza E, de Viedma DG, (2008). Advanced survey of tuberculosis transmission in a complex socioepidemiologic scenario with a high proportion of cases in immigrants. Clin Infect Dis 47:8–14.
4. Centers for Disease Control and Prevention, (2007). Trends in tuberculosis incidence – United States 2006. MMWR Morb Mortal Rep 56:245–250.
5. World Health Organization, (2006). The global plan to stop TB 2006–2015. World Health Organization, Geneva, Switzerland.
6. World Health Organization, (2009). Global tuberculosis control: epidemiology strategy, financing. World Health Organization Report, Geneva, Switzerland.
7. Ramkumar D, La Brecque DR, (2003). Drug-induced liver disease and environmental toxins. In: (eds) Zakin D, Boyer TD; Hepatology: a textbook of liver disease; 4th Edition, Saunders, Philadelphia, p. 755–838.
8. Altman C, Biour M, Grange J, (1993). Hepatic toxicity of antitubercular agents. Role of different drugs, 199 cases. Press Med 22:1212.
9. Dickinson, D, Bailey WC, Hinoschowitz BI, Soony SJ, Leslie MD, Hodgkin MM, (1981). Risk factor for isoniazid (INH)-induced liver dysfunction. J Clin Gastroenterol 3:271–279.
References

10. Raviglione MC, O’Brien RJ, (2008). Tuberculosis. In: (eds) Fauci AS, Braunwald E, Kasper DC, Hauser SC, Longo DC, Jameson JC, Loscalzo J. Harrison’s Principles of Internal Medicine, 17th Edition, McGraw-Hill, New York, p. 1006–1020.

11. Canadian Pharmacists Association, (2009). Isoniazid. In: CPS 2009: Compendium of Pharmaceuticals and Specialties. Can Pharm Assoc, Ottawa, p. 1187–1190.

12. Tostmann A, Boeree MJ, Aanoutse RE, de Lange WL, van der Ven AJ, Dekhuijen R, (2008). Antituberculosis drug-induced hepatotoxicity: concise up-to-date review. J Gastroenterol Hepatol 23:192–2002.

13. Fong IW (ed.), (2009), Emergency issues in head and neck infections. IN: Emerging issues and controversies in infectious disease; Springer, New York, p. 27–46.

14. International Rhinosinusitis Advisory Board, (1992). Infectious rhinosinusitis in adults: classification, etiology and management. Ear Nose Throat J. 76 (72):1–19.

15. Finegold SM, Flynn MJ, Rose FK, Jousimies-Somer H, Jukelaszek C, McTeague M, Wexler HM, Bekowitz E, Wynne B, (2002). Bacteriologic finding associated with chronic bacterial maxillary sinusitis in adults. Clin Infect Dis 35:428–433.

16. Lawson DH, Price BJ, (1982). Adverse reactions to trimethoprim-sulfamethoxazole. Rev Infect Dis 4:429–433.

17. Valeyrie-Allanore L, Roujeau JC, (2008). Epidermal necrosis (Stevens-Johnson Syndrome and toxic epidermal necrosis). In: (eds) Wolff K, Goldsmith LA, Kutz SI, Gilchrist BA, Paller AS, Leffell DJ: Fitzpatrick’s Dermatology in General Medicine, 7th Edition; McGrawHill, New York, p. 349–355.

18. Roujeau JC, Kelly JP, Naldi L, Rzany B, Stern RS, Anderson T, Auquier A, Bastuji-Garin S, Correia O, Locati F, Mockenhaupt M, Paoletti E, Shapiro S, Shear N, Schöpf E, Kaufman DW, (1995), Medication use and the risk of Stevens-Johnson Syndrome or toxic epidermal necrosis. N Engl J Med 333:1600–1608.

19. Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau J-C, Revuz J, Wolkenstein P, (2000). SCORTEN: a severity-of-illness score for toxic epidermal necrosis. J Invest Dermatol 115:149–153.

20. Guégan S, Bastuji-Garin S, Poszepczynska-Guigne E, Roujeau JC, Revuz J (2006). Performance of the SCORTEN during the first five days of hospitalization to predict the prognosis of toxic epidermal necrosis. J Invest Derm 126:272–276.

21. Brown KM, Silver GM, Halerz M, Walaszek, Sandroni A, Gamelli RL (2004). Toxic epidermal necrosis: does immunoglobulin make a difference? J Burn Care Rehabil 25:81–88.

22. Bachot N, Revuz J, Roujeau JC (2003). Intravenous immunoglobulin treatment for Steven-Johnson syndrome and toxic epidermal necrosis: prospective non-comparative study showing no benefit in mortality or progression. Arch Dermatol 139:33–36.

23. Berris K (2009). Adverse events – physician-prescried opioids. Risk identification for all physicians. April 2009; Ri0915E. CMPA website: www.cmpa-acpm.ca

24. Straus SE, Oxman MN, Schmader KE (2008). Varicella and Herpes Zoster. IN (eds): Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paker AS, Leffell DJ: Fitzpatrick’s Dermatology in General Medicine, 7th Edition, McGraw-Hill Medical, New York, p. 1885–1898.

25. Choo PW, Donahue JG, Manson JE, Platt R, (1995). The epidemiology of varicella and its complications. J Infect Dis 172:706–712.

26. Preblud SR (1986). Varicella complications and cost. Pediatrics; 78 (suppl): S728–S735.

27. Feldman S, Hughes WT, Daniel CB (1975). Varicella in children with cancer.: seventy seven cases, Pediatrics; 56:3988–397.

28. Locksley RM, Floumry N, Sullivan KM, Myers JD (1985). Infection with varicella zoster virus after marrow transplantation. J Infect Dis 152:1172–1181.

29. Weller TH (1983). Varicella and herpes zoster: changing concepts of the natural history, control and importance of a not-so-benign virus (first of two parts). N Engl J Med 309:1362–1368.

30. Frey FJ, Speck RF (1992). Glucocorticoids and infection. Schweiz-Med-Wochenschr 122:137–144.
31. Arcuri LB, Cashman LD, Cassaro AT, Kostick JH, Hsiung JRS, Wolfe KR (2009). Hormones and synthetic substitutes: adrenals. In AHFS Drug Information Am Soc Health Sys Pharmacists. Bethesda, MD, p. 3036–3128.
32. Balow JE, Hurley DL, Fauci AS (1975). Immunosuppressive effects of glucocorticosteroids: differential effects of acute vs chronic administration on cell-mediated immunity. J Immunol 114:1072–1076.
33. Schimmer BP, Parker KL (2005). Adrenocorticotropic hormone, adrenocortical steroids and their synthetic analogs: inhibitors of synthesis and actions of adrenocortical hormones. IN: (eds) Brunton LL, Lazo JS, Parker KL: Goodman & Gilman’s: The Pharmacological Basis of Therapeutics, 11th Edition, McGraw Hill, New York, p. 1587–1612
34. Weller TH (1983). Varicella and herpes zoster: changes in concepts of natural history, control and importance of a not-so-benign virus (second of two parts). N Engl J Med 309:1434–1440.
35. Zaia JA (1981). Clinical spectrum of varicella-zoster virus infection. IN: (eds) Nahmias AJ, Dowdle WR, Schinazi RE: The human herpesviruses: an interdisciplinary perspective; Elsevier, p. 10–19.
36. Miliauskas JR, Webber BL (1984). Disseminated varicella at autopsy in children with cancer. Cancer 53:1518–1525.
37. Patti ME, Selvaggi KJ, Kroboth FJ (1990). Varicella hepatitis in the immunocompromised adult: a case report and review of the literature. Am J Med 88:77–80.
38. Sherman RA, Silva J Jr. Gandour-Edwards R (1991). Fatal varicella in an adult: case report and review of gastrointestinal complications of chickenpox. Rev Infect Dis 13:424–427.
39. Maillot C, Riachi G, Francois A, Ducrotte P, Lerebours E, Hemet J, Colin R (1997). Digestive manifestations in an immunocompetent adult with varicella. Am J Gastroenterol 92:1361–1363.
40. Johnson GN (1940). Visceral lesions associated with varicella. Arch Pathol 30:292–307, 13.
41. Marshak RH, Lindwern AE (eds), (1976), in: The human herpesviruses: an interdisciplinary perspective; Saunders, Philadelphia, p. 487–496.
42. Bardhan KD (1978). Cimetidine in “chickenpox esophagitis”. BMJ 1:370 (letter).
43. Gill RA, Gebhard RL, Dozeman RL, Summer HW (1984). Shingles esophagitis: endoscopic diagnosis in two patients. Gastrointest Endosc 30:26–27.
44. Wallace MR, Bowler WA, Murray NB, Brodine SK, Oldfield III EC (1992). Treatment of adult varicella with acyclovir. A randomized placebo-controlled trial. Ann Intern Med 117:358–363.
45. Balfour HH, Bean H, Laskin OL, Ambinder RF, Myers JD, Wade JC, Zaia JA, Aeppli D, Segreti AC, Keeney RF (1983). Acyclovir halts progression of herpes zoster in immunocompromised patients. N Engl J Med 308:1448–1453.
46. Shepp DH, Dandliker PS, Meyers JD (1986). Treatment of varicella-zoster virus infections in severely immunocompromised patients. N Engl J Med 314:208–212.
47. Haake DA, Zakowski PC, Haake DL, Bryson YJ (1990). Early treatment with acyclovir for varicella pneumonia in otherwise healthy adults: retrospective controlled study and review. Rev Infect Dis 12:788–797.
48. Escalante P (2009). In the clinic: tuberculosis. Ann Intern Med 150: ITC 6-1-14.
49. Oxman MN, Levin MJ, Johnson GR, Schmader KE, Strauss SE, Gelb LD, Arbeid RD, Simberkoff MS, Gershon AA, et al, for the Shingles Prevention Study Group (2005). A vaccine to prevent herpes zoster and postherpetic neuralgia in older patients. N Engl J Med 352 V:2271–2284.
50. Yeung CY, Liang DC (1992). Varicella vaccine in children with acute lymphoblastic leukaemia and non-Hodgkin lymphoma. Pediatr Hematol Oncol 9:29–34.
51. Kroger AT, Atkinson WL, Marcuse EK, Pickering LK (2006). General recommendations on immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR:53(RR15):1–48.