Appendix 1

Diagram 1: Examples of comments for clinical question 1

Example 1: The directions for use of hydroxychloroquine sulfate tablets (Fenle, 100 mg tablet) indicate that it is not a suitable medication for children, while the directions for hydroxychloroquine sulfate tablets (Saineng, 200 mg tablet) indicate that it should not be given to children under 6 years of age. Therefore, is it reasonable for clinicians to prescribe hydroxychloroquine sulfate tablets (Saineng, 200 mg tablet) to children over 6 years of age?

Comment: If the clinician can provide the drug instructions for hydroxychloroquine sulfate tablets (Saineng, 200 mg tablet) and give a reasonable explanation for their use, the prescription can be considered reasonable. Following this, prescription comment systems should update the drug instructions for related medications.

Example 2: According to the directions, the maximum dose of sodium bicarbonate tablets produced by Beijing Yanjing is 3 g/day, while that of sodium bicarbonate tablets produced by Tianjin Lisheng is 6 g/day. For patients with hyperuricemia, the clinician prescribed sodium bicarbonate tablets produced by Beijing Yanjing with a dose of 1.5 g Tid. Is this prescription reasonable?

Comment: Prescribing sodium bicarbonate tablets (Beijing Yanjing) at 1.5 g Tid, equivalent to 4.5 g/day, exceeds the maximum dose recommended by Beijing Yanjing. If the prescriber provides a sodium bicarbonate tablet recommendation (Tianjin Lisheng) and gives a reasonable explanation, the prescription may be considered rational. However, the prescribing clinician should be reminded to follow the manufacturer's recommended dosage of a prescribed drug. After this, the prescription comment system should update the instructions for related drugs.

Diagram 2: Examples of comments for clinical question 2

Example 1: Thalidomide has the same pharmacological mechanism for treating the rheumatic immune conditions of ankylosing spondylitis and Behcet's disease. The Guideline for Diagnosis and Treatment of Ankylosing Spondylitis issued by China in 2010 (13) recommends a 50–100 mg/night dose of thalidomide. The Guideline for Diagnosis and Treatment of Behcet's Disease issued by China in 2011 (14) recommends that thalidomide be taken at 25–50 mg Tid. If patients with ankylosing spondylitis are unable to tolerate a thalidomide dose of 50–100 mg, clinicians may prescribe thalidomide at 25 mg 3 times a day, according to the guidelines for Behcet's disease. Is this prescription reasonable?

Comment: According to the leaflet, thalidomide is used in the treatment of erythema nodosum leprosum in China. The use of thalidomide in the treatment of Behcet's disease and ankylosing spondylitis is off label. There is no evidence supporting a thalidomide dosage of 25 mg 3 times daily for the treatment of ankylosing spondylitis, so these prescriptions may be judged as unreasonable.

Diagram 3: Examples of comments for clinical question 3

Example 1: According to the instructions for use of ferrous succinate tablets, pregnant women should take 2 tablets twice a day for an iron supplement of 120 mg/day. According to the Guideline for Diagnosis and Treatment of Iron Deficiency and Iron-Deficiency Anemia during Pregnancy issued by the Chinese Society of Perinatal Medicine in 2014, pregnant women with iron-deficiency anemia should take iron supplements at 100–200 mg/day. Clinicians should prescribe 2 tablets of ferrous succinate 3 times a day in order to supplement pregnant women with 180 mg of iron per day. The dose of this prescription is in line with the guideline but beyond the drug manufacturer's recommended dosage. Is the prescription therefore unreasonable?

Comment: The Guideline for Diagnosis and Treatment of Iron Deficiency and Iron-Deficiency Anemia during Pregnancy issued by the Chinese Society of Perinatal Medicine in 2014 (15) (guideline quality: moderate) recommends that pregnant women with iron-deficiency anemia receive a maximum iron dose of 200 mg/day. A prescribed dose of 180 mg/day of iron supplements is in line with the guideline and can be considered reasonable.

Example 2: Rheumatoid arthritis is not an indication for methotrexate. Is it unreasonable for clinicians to prescribe methotrexate for patients with rheumatoid arthritis as recommended by the Chinese Guideline for the Diagnosis and Treatment of Rheumatoid Arthritis issued by the Chinese Rheumatology Association in 2018?

Comment: The Chinese Guideline for the Diagnosis and Treatment of Rheumatoid Arthritis issued by the Chinese Rheumatology Association in 2018 (16) (guidelines quality: high) recommends methotrexate as the preferred drug for treating rheumatoid arthritis (strongly recommended based on high-quality evidence). Likewise, recent guidelines issued by several international academic organizations in the field of rheumatic disease study, including the American College of Rheumatology (ACR), the European League Against Rheumatism (EULAR), and the Asia Pacific League of Associations for Rheumatology (APLAR) (17-19) (guideline quality: high) all have consistently identified methotrexate as the preferred treatment for patients with rheumatoid arthritis. In summary, the evidence of methotrexate for the treatment of rheumatoid arthritis is sufficient, so the prescription is reasonable.

Example 3: Pregnancy is a contraindication in diazepam's drug label. The Guideline for the Management of Hypertensive Disorders of Pregnancy issued by the Society of Obstetrics and Gynecology from the Chinese Medical Association in 2015 states that diazepam administered orally or by intramuscular injection before bed can help pregnant women relieve the symptoms of mental tension and anxiety, improve sleep, and prevent and control eclampsia. Is it unreasonable for clinicians to prescribe diazepam for pregnant women?

Comment: Diazepam is recommended for use during pregnancy by the Guideline for the Management of Hypertensive Disorders of Pregnancy issued by the Society of Obstetrics and Gynecology from the Chinese Medical Association in 2015 (20) (guideline quality: high) and the Guideline for Epilepsy in Pregnancy issued by the Royal College of Obstetricians and Gynaecologists in 2016 (21). Teratogenic effects of diazepam have not been observed in clinical practice, so the prescription can be judged as reasonable.

Diagram 4: Examples of comments for clinical question 4

Example 1: The approved maximum dose of pantoprazole is 160 mg/day. However, in practice, clinicians may sometimes prescribe pantoprazole at 200–240 mg/day to patients with severe acute gastrointestinal bleeding. Domestic guidelines do not recommend using high doses of pantoprazole in patients with acute gastrointestinal bleeding, so is this prescription unreasonable?

Comment: The Clinical Guideline for Acute Upper and Lower Gastrointestinal Bleeding issued by the Scottish Intercollegiate Guidelines Network (SIGN) in 2008 (22) (guideline quality: high) recommends that an intravenous injection of high-dose proton pump inhibitors (infusion of 8 mg/hour for 72 hours following an initial intravenous dose of 80 mg) can be used for patients receiving endoscopic treatment for peptic ulcer bleeding. The guideline issued by the American College of Gastroenterology (ACG) in 2012 (23) (guideline quality: high) indicates that an intravenous injection of pantoprazole before endoscopy (infusion of 8 mg/hour following an initial intravenous dose of 80 mg) can reduce the risk of massive bleeding during endoscopic examination and treatment; the ACG further recommends injecting proton pump inhibitor e after successful hemostasis under endoscopy is reached for patients with active bleeding, exposed blood vessels, or adherent blood clots (infusion of 8 mg/hour for 72 hours following an initial intravenous dose of 80 mg). According to a 2007 randomized controlled trial (n=153) from Hong Kong, China (24), for patients with bleeding from endoscopic treatment of peptic ulcer, the use of pantoprazole by intravenous infusion (following an initial intravenous injection of 80 mg of pantoprazole and an 8 mg/hour continuous infusion lasting for 3 days) or an intravenous injection (following an initial 80 mg intravenous injection of pantoprazole and an infusion of 40 mg every 12 hours for 3 days) can reduce the chance of patient rebleeding (quality of evidence: low). In summary, a high dose (>160 mg) of pantoprazole can be used in patients with acute gastrointestinal bleeding, and there is sufficient evidence to judge that the prescription is reasonable.

Example 2: Liraglutide is approved domestically for the treatment of type 2 diabetes. Is it rational for physicians to also use liraglutide to treat obesity in nondiabetic patients?

Comment: In China, guidelines and textbooks do not provide recommendations or instructions for the treatment of obesity by liraglutide, but it is sometimes used to treat obesity in domestic clinical practice. The Guideline of Pharmacological Management of Obesity issued by the European Endocrine Society in 2015 (25) (guideline quality: high) and the Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology in 2019 (26) (guideline quality: high) both recommend the use of liraglutide for the treatment of obesity. The Food and Drug Administration has approved the use of liraglutide for patients with a BMI above 27 kg/m^2 and at least 1 complication of obesity (such as high blood pressure, type 2 diabetes, hyperlipidemia) or those who have simple obesity with a BMI above 30 kg/m^2. In conclusion, there is sufficient evidence for the treatment of obesity with liraglutide, so the prescription is reasonable.

Diagram 5: Examples of comments for clinical question 5

Example 1: Mycophenolate mofetil is not approved for the treatment of lupus erythematosus in China. The Guideline for the Diagnosis and Treatment of Systemic Lupus Erythematosus (SLE) issued by the Chinese Rheumatology Association in 2010 recommends that patients with SLE should take mycophenolate mofetil at 0.5–1 g 2 times day. The Guideline for Diagnosis and Treatment of Cutaneous Lupus Erythematosus (CLE) issued by the Chinese Society of Dermatology in 2019 recommends that patients with CLE should take mycophenolate mofetil, 35 mg/kg/day, divided into 2 doses. If one patient with lupus erythematosus (LE) weighs 70 kg, the CLE guideline allows for a 2.5g/day dose of mycophenolate mofetil, but the dose is more than that recommended by the SLE guideline. Is it reasonable for clinicians to prescribe 2.5 g of mycophenolate mofetil per day for lupus erythematosus patients?

Comment: The quality of the SLE guideline from 2010 (27) is low, while the quality of the 2019 CLE guideline (28) is moderate. Prescribing 2.5g/day of mycophenolate mofetil to patients with a body weight of 70 kg is consistent with the CLE guideline's recommendation of mycophenolate mofetil at 35 mg/kg/day, and as this guideline is of higher quality, the prescription may be judged as reasonable.

Diagram 6: Examples of comments for clinical question 6

Example 1: Tofacitinib is approved in China for the treatment of adult patients with moderate to severe active rheumatoid arthritis for whom methotrexate is ineffective or intolerable. Is it reasonable for a clinician to prescribe oral tofacitinib to patients with severe psoriasis, 5 mg 3 times a day?

Comment: There is no recommendation for the treatment of psoriasis by tofacitinib in either domestic or international guidelines. In 2018, a SR from Taiwan, China, (n=2,724) (29) showed that compared to a placebo, tofacitinib significantly reduced the Psoriasis Area and Severity Index score of moderate to severe plaque psoriasis patients and improved the Physician's Global Assessment; however, tofacitinib was also associated with higher cholesterol levels and higher rates of upper respiratory infections. The differences in other adverse reactions between the 2 groups was not statistically significant (quality of evidence: moderate). Thus, there is sufficient evidence for the treatment of severe psoriasis with tofacitinib, so the prescription can be considered reasonable.

Example 2: For some patients with inflammatory arthritis, a specific diagnosis often cannot be established in the weeks and months following the initial onset of symptoms, but medication is required to reduce both patient symptoms and the progression of the disease. There are currently no guidelines for the treatment of inflammatory multijoint disease. Is it unreasonable for clinicians to prescribe hydroxychloroquine sulfate and leflunomide to patients diagnosed with inflammatory multijoint disease?

Comment: There is no recommendation for the use of hydroxychloroquine sulfate combined with leflunomide in the treatment of inflammatory arthritis in either domestic or international guidelines, and no systematic evaluations or original studies about the combination of hydroxychloroquine sulfate and leflunomide in the treatment of inflammatory arthritis have been found. In conclusion, evidence for the treatment of inflammatory multijoint disease with hydroxychloroquine sulfate combined with leflunomide is lacking, so the prescription should be judged as unreasonable.

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