An evidence-based medicine approach to optimising medication therapy in a patient with *Clostridium difficile* infection

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This paper is based on the Best Scenario presentation at the SAAHIP Conference 2019

Introduction

Adverse drug reactions (ADRs) are one of the most common causes of morbidity and mortality and approximately 70% of ADRs can be prevented. In Europe, 6.5% of hospitalisations are due to ADRs, quite similar to the estimated prevalence in South Africa (6.3%).[1,2]

Globally a rise in antimicrobial resistance is evident. Approximately 9.7% of multidrug-resistant tuberculosis (TB) patients have extensively drug-resistant TB (XDR-TB). Approximately 65% of *Escherichia coli* isolates are resistant to ciprofloxacin. Patients with methicillin-resistant *Staphylococcus aureus* (MRSA) have a 64% higher risk of mortality compared to patients with methicillin-sensitive *Staphylococcus aureus*.[3,4]

Pharmacists have the potential to reduce ADRs experienced by patients, as well as to lead the fight against antimicrobial resistance, by means of the provision of pharmaceutical care. Pharmaceutical care is not a specialist function but is a universal service that can be delivered by every pharmacist. According to Helper and Strand's 1990 definition, "pharmaceutical care is the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve patients' quality of life".[5] Thus our approach should be patient-centred, guided by the pharmaceutical care process, as depicted in Figure 1.

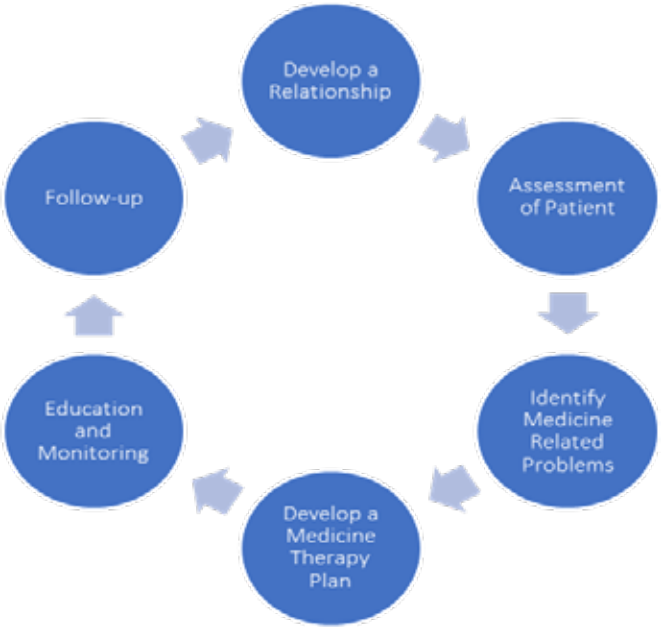

Figure 1: Pharmaceutical care process[6]

Case presentation

This case was encountered at Tygerberg Hospital, a public sector tertiary academic hospital in South Africa. The case emphasises the role of the pharmacist in optimising medication therapy to improve patient care, following an evidence-based medicine approach.

Patient presentation

Mrs JH is a 75-year-old female with a BMI of 20 kg/m^2. Her medical history included type 2 diabetes mellitus, hypertension, peptic ulcer disease and an unrepaired hernia.

She was referred from a private hospital with pain in her left arm after a low energy fall at home and required surgery for repair of a fractured arm. During her hospital admission she was treated for a community-acquired urinary tract infection and hospital-acquired pneumonia.

The current complaint was severe, persistent, loose and foul-smelling diarrhoea, not responding to loperamide. *Clostridium difficile* infection (CDI) was a possible diagnosis.

Clostridium difficile infection

CDI is defined as having ≥3 loose stools within 24 hours with a positive *Clostridium difficile* toxin test, toxigenic positive test or the identification of pseudomembranous colitis on colonoscopy.[7] *Clostridium difficile* is a Gram-positive anaerobic, spore forming bacteria accounting for 30% of antibiotic-associated diarrhoea. It distorts the normal gut flora and creates an ideal environment to produce toxins, thus causing extensive inflammation of the colon and tissue damage.[8,9]

CDI is a common healthcare-associated infection and one in five patients will experience recurrence.[8] The risk factors for CDI are summarised in Table 1.[7] Studies have also shown that the use of proton pump inhibitors and laxatives may be risk factors for CDI.[9,10]

Severe CDI is defined as an episode of CDI with severe colitis or a complicated course of disease, with significant systemic toxin effects and shock, resulting in the need for ICU admission, colectomy or death. Those over the age of 65 years with serious co-morbid conditions, immunocompromised patients and those admitted to the intensive care unit, all have an increased risk for severe CDI.[11]

According to Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) guidelines, CDI should

Table 1: Risk factors for CDI [7,9,10]

Factor
Elderly ≥ 65 years
Immunocompromised patients e.g. cancer patients receiving chemotherapy
Antibiotic use in the last 90 days: • Penicillin • Beta-lactam inhibitor combinations • Cephalosporins: third (ceftriaxone, cefotaxime, cefixime) and fourth generation (cefepime) • Clindamycin

be treated based on severity. Treatment options for CDI are described in Table 2 below.[7]

Oral vancomycin is not available in South Africa; however, the injectable product can be used for oral administration. No therapeutic drug monitoring or dosage adjustment are required with oral administration. During pulse therapy, vancomycin is administered as 125 mg orally twice a week for one week, followed by 125 mg orally once a week for one week, and then 125 mg orally every second to third day for 2-8 weeks.[7] Fidaxomicin reduces the recurrence rate of CDI,[7] but is not available in the South African public sector due to its high acquisition cost. The private sector single exit price is R14 950 for 20x200 mg tablets. Faecal transplants are only done under strict trial conditions in South Africa.

Non-pharmacological treatment includes adequate rehydration therapy with intravenous normal saline and oral rehydration solution.[12]

Loperamide, an anti-motility agent, is contra-indicated in CDI as it increases the risk for toxic megacolon. In a study conducted in South Africa, 44% of prescription charts that were reviewed for CDI showed that loperamide had been prescribed.[13] Once CDI was confirmed, loperamide was discontinued in only 22% of patients.

Clinical dilemma

Mrs JH was receiving vancomycin 500 mg 6 hourly orally as empiric therapy for the treatment of CDI. According to the evidence described above, her risk factors for severe CDI included age and exposure to broad spectrum antibiotics. However, the diagnosis was not yet confirmed. Intravenous sodium chloride for rehydration therapy increased the risk of infection and oral therapy was tolerated.

The following medication-related problems were identified on review of Mrs JH's prescription chart in the ward:

1. The dosage of vancomycin was too high for the treatment of severe CDI
2. Mrs JH required alternative therapy for the prevention of dehydration

During a discussion with the medical team the following was recommended:

1. Confirmation of CDI with a stool sample
2. Reduce vancomycin to 125 mg orally every 6 hours and treat for a total of 10 days
3. Discontinue intravenous sodium chloride. Initiate oral rehydration solution

CDI was confirmed with a stool sample (*Clostridium difficile* antigen positive/toxin negative; toxigenic *Clostridium difficile* positive). Therapy was appropriately adjusted, based on confirmation of diagnosis, SHEA/IDSA[9] recommendations and available therapy at the hospital, to vancomycin 125 mg orally every 6 hours. Rehydration therapy was optimised. Mrs JH's medication-related problems were thus resolved, and medication therapy was optimised by a pharmacist being part of a medical team and practising evidence-based medicine at ward level.

Patient outcome

Once therapy was completed, the diarrhoea resolved, and Mrs JH was discharged from hospital. Counselling of the patient and family included good hand hygiene practices and monitoring for symptoms of diarrhoea in the future.

Lessons learnt and recommendations for future

Pharmacists can provide quality patient care through practising pharmaceutical care at ward level. A comprehensive history taken by a pharmacist is valuable in guiding medicine management and a pharmacist practising evidence-based medicine can optimise patient health outcomes. Being experts in medicine, they should be given the opportunity to apply their skills at ward level and to participate in patient ward round discussions, with a clear focus on medication therapy. Antimicrobial stewardship in healthcare facilities should be led by pharmacists, not only to reduce antibiotic utilisation and thus

Table 2: Recommended treatment based on CDI severity[7]

Severity classification	Clinical and laboratory considerations	Treatment options
Initial, non-severe	White blood cell count ≤ 15 x 10^9/L **PLUS** Serum creatinine <132 µmol/L	Metronidazole 500 mg 8 hourly orally daily for 10 days, **OR** Vancomycin 125 mg 6 hourly orally for 10 days, **OR** Fidaxomicin 200 mg 12 hourly orally for 10 days
Initial, severe	White blood cell count ≥ 15 x 10^9/L **OR** Serum creatinine >132 µmol/L	Vancomycin 125 mg 6 hourly orally for 10 days, **OR** Fidaxomicin 200 mg 12 hourly orally for 10 days
Initial, fulminant	Hypotension, shock, ileus or megacolon	Vancomycin 500 mg 6 hourly orally for 10 days **PLUS** Metronidazole 500 mg 8 hourly intravenously for 10 days
Recurrence		Vancomycin 125 mg 6 hourly orally for 10 days, **OR** Pulse vancomycin therapy, **OR** Fidaxomicin 200 mg 12 hourly orally for 10 days, **OR** Faecal microbiota transplant

resistance, but to optimise medication therapy and reduce antibiotic-associated adverse events.

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