BC Provincial Antimicrobial Clinical Expert Group (PACE)

Sequential Antimicrobial Therapy in Adults – Best Practice Recommendations

SITUATION-BACKGROUND-ASSESSMENT-RECOMMENDATION (SBAR) – JUNE 2021

SITUATION

1. REQUEST

At the October 2019 Provincial Antimicrobial Clinical Experts (PACE) group planning meeting, development of best practice recommendations for sequential antimicrobial therapy (SAT) was prioritized for 2019-2020. Although many health authorities have approved and implemented SAT recommendations, guidelines, or clinical practice standards, it was felt that common best practice recommendations could be used to update and standardize British Columbia Health Authority (BCHA) practice.

The purpose of this SBAR is to outline SAT evidence-based best practice recommendations including eligible antimicrobials, patient selection, pharmacist authority, and measurement of outcomes.

BACKGROUND

Sequential antimicrobial therapy (SAT) refers to the replacement of a parenteral version of a medication with its oral counterpart.[1] In contrast, step-down therapy refers to converting from an injectable to an oral agent in an another class (e.g. ceftazidime IV to ciprofloxacin PO) or to a different medication in the same class where the dose, frequency or spectrum of antimicrobial activity is may not be exactly the same (e.g. piperacillin-tazobactam IV to amoxicillin-clavulanate PO). SAT has been best described using conversions from parenteral to highly oral bioavailable antimicrobials. Table 1 lists the current formulary parenteral antimicrobials with highly oral bioavailable counterparts (>70%) or for azithromycin, a long half-life and high tissue concentrations, that are well tolerated upon oral administration and have clinical data supporting use in SAT. For most infections and in patients without contraindications (see Table 2), highly oral bioavailable antimicrobial agents can be used for initial therapy.

The Infectious Diseases Society of America (IDSA) / Society for Healthcare Epidemiology of America (SHEA) 2016 Implementing an Antimicrobial Stewardship Program: Guidelines recommends promotion of intravenous (IV) to oral (PO) antimicrobial conversion to increase use of oral antimicrobial agents, reduce costs, and reduce length of hospital stay.[2]

Table 1. BC Health Authority Drug Formulary Antimicrobial Agents Suitable for Sequential Antimicrobial Therapy (SAT)
(With dose adjustment in renal impairment, as applicable)

Antimicrobial Agent	Bioavailability	Usual IV dose	PO conversion	Comments
Azithromycin	37%	500 mg Q24H	500 mg Q24H	Reduced oral bioavailability is usually compensated by enhanced tissue penetration and a long half-life
Ciprofloxacin	70-80%	400 mg Q12H 400 mg Q8H*	500-750 mg Q12H**	*400 mg IV Q8H preferred for septic shock, especially when *Pseudomonas aeruginosa* is a potential pathogen. **Use 750 mg PO dose for *Pseudomonas aeruginosa* and other severe infections.

Antimicrobial Agent	Bioavailability	Usual IV dose	PO conversion	Comments
				Note: Enteral feedings need to be discontinued for 1-2 hours prior to and after ciprofloxacin administration
Clindamycin	90%	300 mg Q6-8H	300 mg Q6-8H	***maximum oral dose is 1.8 g/day
		450 mg Q6-8H or 600 mg Q8H	450 mg Q6-8H*** or 600 mg Q8H***	
Fluconazole	90%	200 mg DAILY	200 mg DAILY	For serious infections, a fluconazole 800 mg IV or PO loading dose recommended
		400 mg DAILY	400 mg DAILY	
Linezolid	100%	600 mg Q12H	600 mg Q12H	Restricted Formulary Antibiotic
Levofloxacin	99%	500 mg Q24H	500 mg Q24H	
		750 mg Q24H	750 mg Q24H	
Metronidazole	100%	500 mg Q12H	500 mg Q12H	†Use 500 mg IV/PO Q8H/TID for *Clostridioides/Clostridium difficile* infections
		500 mg Q8H†	500 mg Q8H†	
Moxifloxacin	90%	400 mg Q24H	400 mg Q24H	
Trimethoprim-sulfamethoxazole	80-100%	80/400 mg Q12H	80/400 mg Q12H	††Higher doses may be required for some infections (e.g. *Pneumocystitis* pneumonia, or *Stenotrophomonas maltophilia*, *Nocardia* infections)
		160/800 mg Q12H††	160/800 mg Q12H††	
Voriconazole	96%	200 mg Q12H	200 mg Q12H	Restricted Formulary Antifungal Agent IV dose: 3-6 mg/kg IV Q12H, depending on indication
		300 mg Q12H	300 mg Q12H	

Evidence Supporting Clinical Efficacy and Safety

Practice guidelines support SAT to manage a wide range of serious infections in hospitalized patients. The American Thoracic Society (ATS) / IDSA 2019 Diagnosis and Treatment of Adults with Community-acquired Pneumonia (CAP) practice guidelines recommend azithromycin 500 mg Q24H plus a β-lactam antibiotic, such as ceftriaxone 1-2 g IV Q24H or cefotaxime 1-2 g IV Q8H, to empirically treat inpatients.[3] Azithromycin is typically added to a β-lactam antibiotics in severe CAP (CRB-65 greater than 2) or if there is high suspicion of pathogens not susceptible to β-lactam antibiotics. Pharmacokinetic studies indicate oral azithromycin, despite having an oral bioavailability of 37%, achieves high monocyte / macrophage and intracellular and extracellular pulmonary concentrations. This is complimented with a long half-life of 2-3 days (48-72 hours), which allows for short-course CAP treatment of 3-5 days.[4,5,6] Furthermore, early randomized controlled trials (RCTs) with azithromycin monotherapy demonstrated the effectiveness of oral therapy or SAT to treat hospitalized patients with CAP. [7,8,9] Subsequent RCTs have supported β-lactam antibiotic combination therapy for CAP with oral azithromycin or azithromycin SAT in eligible inpatients.[10,11,12,13]

The ATS / IDSA 2019 guidelines also indicate that fluoroquinolones, such as oral levofloxacin and moxifloxacin, can be used to treat CAP in hospitalized patients with contraindications β-lactam antibiotic therapy. Feasibility and effectiveness of SAT using IV to PO fluoroquinolones in moderate to severe CAP in hospitalized patients has been demonstrated in observational and randomized clinical trials. [14-21] As well, SAT using oral linezolid, is indicated for CAP or nosocomial pneumonia caused by methicillin-resistant *Staphylococcus aureus* (MRSA).[22]

The Association of Medical Microbiologists and Infectious Diseases Physicians (AMMI) of Canada 2010 practice guidelines for surgical intra-abdominal infections recommend several antibiotic treatment options for empirical treatment of community-acquired intra-abdominal infections with low to moderate severity (APACHE II score

lower than 15).[23] A β-lactam antibiotic, such as ceftriaxone, plus IV to PO metronidazole, is the preferred option in BC health authorities. In patients who have contraindications to a β-lactam antibiotic therapy, SAT using ciprofloxacin plus metronidazole can be used. . This recommendation has been confirmed in a randomized controlled trial.[24] The IDSA 2011 clinical practice guidelines for treatment pyelonephritis recommend oral ciprofloxacin with or without an initial 400 mg dose of IV ciprofloxacin.[25] Feasibility and effectiveness of SAT for treatment of urinary tract infections (UTIs), with or without associated bacteremia, has been demonstrated in observational trials.[21,26]

The IDSA 2009 clinical practice guidelines for management of candidiasis recommend fluconazole for treatment of candidemia or invasive candidiasis in nonneutropenic patients who are not critically ill, have not had recent exposure to azole, and do not have infection with *Candida glabrata or Candida krusei*. Voriconazole is indicated for treatment of selected cases of candidiasis due to *Candida krusei* or voriconazole-susceptible *Candida glabrata*.[27] Due to excellent bioavailability, both fluconazole and voriconazole may be given orally for these indications. Feasibility and effectiveness of this approach has been confirmed in observation trials. [28,29]

Trimethoprim-sulfamethoxazole (TMP-SMX) has an oral bioavailability 80-100% and is suitable for SAT.[30,31] The IV formulation is typically reserved for serious systemic infections where higher doses are sometimes used. For example, TMP-SMX 5-10 mg/kg/day (trimethoprim component)(in divided doses) is the drug of choice for pulmonary infections caused by *Nocardia asteroides* complex.[32,33] TMP-SMX 15-20 mg/kg/day (trimethoprim component)(divided doses) is the drug of choice for *Pneumoncystits jiroveci* pneumonia in both HIV and other immunocompromised individuals.[34,35] Similarly, TMP-SMX 15 mg/kg/day (trimethoprim component)(divided doses) is indicated for serious *Stenotrophamonas maltophilia* infections (e.g. pneumonia, bacteremia).[36] SAT has not as well studied for TMP-SMX for high dose regimens, but may be suitable for treatment of nocardosis and *Pneumocystitis jiroveci* pneumonia, where the treatment course is lengthy.[32,33,34,35]

Finally, though not mentioned in clinical practice guidelines, clindamycin, with oral bioavailability of 90%, is suitable for SAT as demonstrated in an observation trial in patients with respiratory tract and surgical site infections.[37] Due to gastrointestinal intolerance, the maximum clindamycin oral dose is 1.8 g/day.[38]

Other Benefits of SAT

Benefits of SAT include improved patient comfort, less risk of infusion- or catheter-related adverse events (e.g. infection, phlebitis), cost savings (antimicrobial costs, IV sets and pumps, preparation and administration time), and earlier discharge from hospital without compromising patient outcomes.[1, 9,17,18,19,20,21, 39,40,41] For example, in a 2005 observational, study by Ho BP et al., conducted at Vancouver General Hospital, implementation of a pharmacist-managed SAT program demonstrated reduced IV ciprofloxacin use (from 47% to 36%, p=0.0005) and resulted direct drug cost savings of $93/patient.[21] In a 1997 study by Przbylski et al., a prospective program to convert patients from IV to PO ciprofloxacin realized $173 USD/patient drug cost acquisition cost savings and $242 USD/patient in cost savings associated with reduced length of stay.[39]

Patient Eligibility

Patient eligibility for SAT is based on ongoing need for antimicrobial treatment, contraindications to oral therapy, and diagnosis.[1] Evaluation of IV antimicrobial therapy is an opportunity to determine if antimicrobial therapy is still required, or if it can be tailored based on culture and sensitivity results. Patients should have no contraindications to oral antimicrobial therapy (Table 2). [1] For patients with shock, poor gastrointestinal perfusion may reduce bioavailability.[1] However, in the absence of shock, lack of clinical improvement is not per se a contraindication to oral therapy as it has no effect on gastrointestinal absorption. For example, a patient with CAP

who does not have contraindications to oral therapy could be empirically prescribed oral moxifloxacin without need to demonstrate clinical improvement.

Table 2. Potential Contraindications to Oral Antimicrobial Therapy

Parameter	Examples
Unable to take antimicrobial orally	Not tolerating other medications, fluids and/or food orally or enterally in hospital for at least 12 hours NPO Nasogastric/oral gastric tube to suction Active gastrointestinal bleeding Difficulty swallowing Loss of consciousness without NG/OG present Recurring emesis
Poorly functioning gastrointestinal tract	Documented ileus or GI obstruction Short GI transit time (e.g. malabsorption syndromes, partial or total gastrectomy, short bowel syndrome)
Shock	Septic shock Receiving vasopressors
Significant drug-drug or drug-enteral formulation interactions that may alter absorption	Ciprofloxacin interactions with continuous enteral feeding formulations (if enteral nutrition cannot be held 1-2 hours before and after administration) Any drug interactions know to increase or decrease antimicrobial concentrations that can lead to toxicity or therapeutic failure

Finally, patients eligible for SAT should not have an infection for which only IV therapy is indicated

Pharmacist-Managed SAT

SAT is typically managed by prescribers (physicians, nurse practitioners), but increasingly by clinical pharmacists.[11,13,17,21] Many BC health authorities, through local pharmacy and therapeutics committees, allow pharmacists involved in direct patient care to implement SAT. Collaborative pharmacist prescribing is also supported by the BC College of Pharmacists.

Outcome Measurement

After implementation of a SAT program, outcomes can be measured using antimicrobial consumption of IV and PO days of therapy/1000 patient-days, defined daily doses/1000 patient days and/or costs.

1. INTERNAL HA CONCERNS

   None expressed

ASSESSMENT

- SAT for highly oral bioavailable medications is clinically effective, safe, cost-effective, improves patient comfort, and results in earlier discharge from hospital.
- Patient eligibility for SAT includes need for antimicrobial continuation, no contraindications to oral antimicrobial absorption, and evidence that the infection can be treated with PO therapy.
- Increasing, clinical pharmacist-managed SAT programs, approved by the pharmacy and therapeutics committee or through a collaborative pharmacist prescribing model, allow initiation of SAT in eligible patients.

1. BUDGET IMPACT ANALYSIS (BIA)

   Table 3 lists the Health Shared Services of BC (HSSBC) contract prices for the IV and PO formulations.

   (NOTE: PROPRIETARY COSTING INFORMATION HAS BEEN REMOVED)

RECOMMENDATION

1. SUMMARY:

A.	Antimicrobials eligible for SAT	Azithromycin, ciprofloxacin, clindamycin, fluconazole, levofloxacin, linezolid, metronidazole, moxifloxacin, trimethoprim-sulfamethoxazole, voriconazole
B.	Patient eligibility for SAT	Able to take antimicrobial orally, no problems with gastrointestinal absorption, no significant drug-interactions
C.	Exclusion criteria	Shock Infections treated with IV antimicrobials only
D.	Pharmacist-managed SAT	Pharmacist authority to initiate SAT in eligible patients be granted by the Health Authority Pharmacy and Therapeutics Committee
E.	Are there any particular implementation issues which need to be addressed (e.g., staff education, staff communication)?	Yes; physician, nurse practitioner, pharmacist, and nurse IV to PO SAT program education is recommended prior to implementation
G.	Should utilization of these drugs be monitored?	Yes; the success of the program should be evaluated annually through measurement of antimicrobial consumption.

2. PROPOSAL

Date	Proposal	Comment
September 24, 2020	PACE group endorses SAT for highly oral bioavailable antimicrobials in eligible patients.	PACE and the Drug Review Subcommittee to partner obtaining stakeholder feedback in October 2020.
May 27, 2021	PACE group finalizes SAT for highly oral bioavailable antimicrobials in eligible patients (post-stakeholder feedback)	

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