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PHARMACY EDUCATION

GameChangers: A Year in Review Part 2

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Disclosure

- Geoff Wall reports the following:
  - Speaker's bureau member for Janssen and La Jolla Pharmaceuticals
  - Off-label use of medication will be discussed during this presentation

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Pharmacist Learning Objectives

Upon successful completion of this course, pharmacists should be able to:

- Classify "Gamechangers" by how they affect practice settings.
- Discuss the selection of each "Gamechanger" topic and how they will impact the provision of patient care.
- Describe possible solutions to clinical problems listed throughout the presentation.
- Assess the clinical trials used to support the content for this presentation.
- Apply the information presented to influence patient care and outcomes at your specific practice site.

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Pharmacy Technician Learning Objectives

Upon successful completion of this course, pharmacy technicians should be able to:

- Classify "Gamechangers" by how they affect practice settings.
- Discuss the selection of a "Gamechanger" topic and how it will impact the provision of patient care.
- Describe opportunities for the advancement of pharmacy technician roles based on information presented.
- Identify the clinical trials used to support the content for this presentation.
- Apply the information presented to influence patient care and at your specific practice site.

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Gamechanger #5

De-escalation of Inhaled Corticosteroids in COPD

Who? When? Why?

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INITIAL PHARMACOLOGICAL TREATMENT

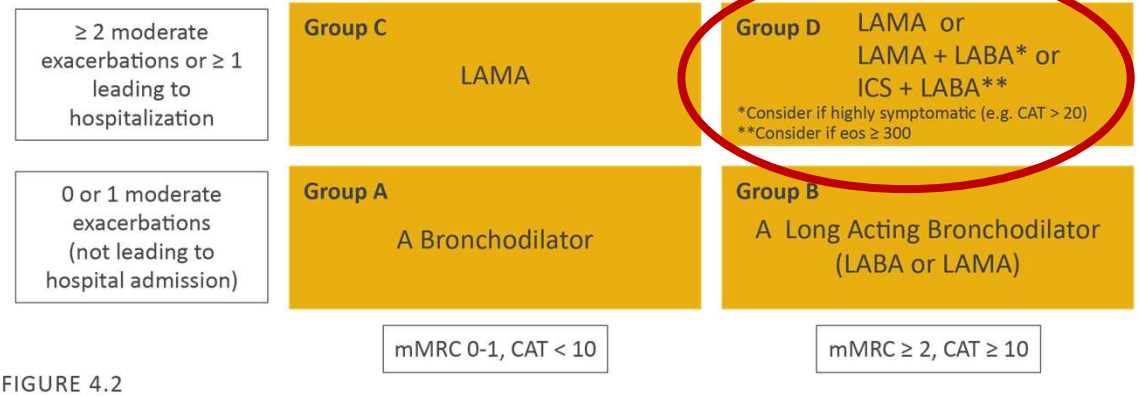

FIGURE 4.2

Global Initiative for Chronic Obstructive Lung Disease Global Initiative for Chronic Obstructive Lung Disease 2021. Goldcopd.org. Accessed 11/5/21

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ANTI-INFLAMMATORY THERAPY IN STABLE COPD

INHALED CORTICOSTEROIDS

- An ICS combined with a LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with exacerbations and moderate to very severe COPD **(Evidence A)**.
- Regular treatment with ICS increases the risk of pneumonia especially in those with severe disease **(Evidence A)**.
- Triple inhaled therapy of LABA/LAMA/ICS improves lung function, symptoms and health status, and reduces exacerbations, compared to LABA/ICS, LABA/LAMA or LAMA monotherapy **(Evidence A)**. Recent data suggest a beneficial effect versus fixed-dose LABA/LAMA combinations on mortality in symptomatic COPD patients with a history of frequent and/or severe exacerbations.

Global Initiative for Chronic Obstructive Lung Disease Global Initiative for Chronic Obstructive Lung Disease 2021. Goldcopd.org. Accessed 11/5/21

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FACTORS TO CONSIDER WHEN INITIATING ICS TREATMENT

Factors to consider when initiating ICS treatment in combination with one or two long-acting bronchodilators (note the scenario is different when considering ICS withdrawal):

· STRONG SUPPORT ·	· CONSIDER USE ·	· AGAINST USE ·
• History of hospitalization(s) for exacerbations of COPD#	• 1 moderate exacerbation of COPD per year#	• Repeated pneumonia events
• ≥ 2 moderate exacerbations of COPD per year#	• Blood eosinophils 100-300 cells/µL	• Blood eosinophils <100 cells/µL
• Blood eosinophils >300 cells/µL		• History of mycobacterial infection
• History of, or concomitant, asthma		

#despite appropriate long-acting bronchodilator maintenance therapy (see Table 3.4 and Figure 4.3 for recommendations);

*note that blood eosinophils should be seen as a continuum; quoted values represent approximate cut-points; eosinophil counts are likely to fluctuate.

Global Initiative for Chronic Obstructive Lung Disease Global Initiative for Chronic Obstructive Lung Disease 2021. Goldcopd.org. Accessed 11/5/21

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Gold Report Statement on ICS Withdrawal

- "Results from withdrawal studies provide equivocal results regarding consequences of withdrawal of lung function, symptoms and exacerbations. Some studies, but not all, have shown an increase in exacerbations and/or symptoms following ICS withdrawal, while others have not."
- "There has been evidence for a modest decrease in FEV1 (approximately 40mL) with ICS withdrawal, which could be associated with increased baseline circulating eosinophil level. A study examining ICS withdrawal on a background of dual bronchodilator therapy demonstrated that both FEV1 loss and an increase in exacerbation frequency associated with ICS withdrawal was greatest among patients with a blood eosinophil count ≥300 cells/µL at baseline."
- "Differences between studies may relate to differences in methodology, including the use of background long-acting bronchodilator medication(s) which minimize any effect of ICS withdrawal."

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Studies Prior to 2014

Did not include long-acting muscarinic antagonists (LAMAs)

Primarily deescalated from:

- LABA + ICS → LABA
- ICS → nothing (placebo)

Showed ICS discontinuation may:

- Cause exacerbations earlier
- Increase number of exacerbations
- Decrease in quality of life

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WISDOM: Withdrawal of Inhaled glucocorticoids and exacerbations of COPD (2014)

Patient Population

- 2488 adults ≥ 40 y/o
- Severe or very severe COPD with ≥1 exacerbation in the last year
- On triple therapy for at least 6 weeks prior to trial

Method of De-escalation: titrate off ICS

- Stepwise reduction of fluticasone dose every 6 weeks
- TDD: 1000mcg → 500mcg → 200mcg → 0mcg (placebo)

Results

- Withdrawal of ICS was noninferior to continuing for prevention of exacerbations
- ICS withdrawal reduced FEV1 by a small amount compared with ICS continuation

Magnussen, Helgo, et al. NEJM 2014, 371:1285–1294

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Sunset: Long-term triple therapy de-escalation to indacteraol/glycopyrronium in patients with COPD

Patient population

- 1053 adults ≥ 40 y/o
- ≤1 moderate or severe exacerbation in the last year
- On triple therapy ≥ 6 months prior to trial

Method of de-escalation

- Cold turkey, no titration

Results

- Direct de-escalation led to a small decrease in lung function, with no difference in exacerbations
- ≥ 300 blood eosinophils/µL had high risk of exacerbation after de-escalation

Chapman KR, et, al. Am J Respir Crit Care Med. 2018;198:329-339.

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Optimizing de-escalation of inhaled corticosteroids in COPD: a systematic review of real-world findings

- Real world studies support findings from WISDOM and SUNSET findings
- Switch from ICS/LABA to LABA/LAMA
  - Reduce risk of exacerbation
  - Increase FEV1
- Switch from triple therapy to LABA/LAMA did not change risk of exacerbation
  - Possibly because triple therapy was inappropriately initiated in most patients
- Triple therapy did not reach minimal clinically important difference over LABA/LAMA with respect to exacerbation risk and lung function
- Patients benefit switching from ICS/bronchodilator to single bronchodilator
- Confirms eosinophil relationship to ICS benefit

Rogliani P, et al. Expert Review of Clinical Pharmacology, 2020;13: 977–990

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Bottom Line

Patients with low baseline eosinophils (<300cells/µL) and stable COPD, no matter the severity, should be considered for ICS de-escalation.

ICS can be stopped without titration but should be monitored closely for significant worsening of symptoms or exacerbation.

A small decrease in FEV1 is expected and this alone should not be considered worsening of symptoms.

What can pharmacy teams do?

- Ask about patients on triple therapy
- Check or ask about blood eosinophil levels
- Provide education on long term ADRs of ICSs

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Gamechanger #6

GI Ulcer update: New H. Pylori guidelines and NSAID use guidelines

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Peptic Ulcer Disease (PUD): Background

- Epidemiology
- About 10% of the US population will have PUD during their lifetime
- Costs in the US exceed $10 billion/yr
- Gastric and Duodenal Ulcers

Lau JY et al. Digestion 2011;84:102–113

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Peptic Ulcer Disease (PUD): Background

- Risk Factors
- Age (especially over age 60)
- Smoking - Increases risk of both DU and GU and impairs healing when PUD is being treated
- NSAID use (accounts for about 25% of acute GI bleeds in the U.S.) - see below
- *Helicobacter pylori* infection - see below
- Hypersecretory states (e.g., Zollinger-Ellison Syndrome)
- Corticosteroids – controversial as data at this point only points to steroids causing PUD in the presence of NSAIDs
- SSRIs? Data points to concomitant risk
- Stress related mucosal disease (SRMD)
- Caffeine - No direct link found

Lau JY et al. Digestion 2011;84:102–113

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2017 ACG Guideline for *H. pylori*

- Treatment Regimens (IN NORTH AMERICA)
- All First line (ALL 14 DAYS):
  - Amoxicillin or Metronidazole + Clarithromycin + PPI
  - Bismuth + Tetracycline + Metronidazole + PPI
    - Preferred in PCN allergic pts, those who have recently received macrolide ABX and those on medications with interaction potential with macrolides
  - Levofloxacin + Amoxicillin + PPI (also used as salvage therapy)
- Treatment failure (ALL patients should be confirmed for eradication)
  - See algorithm

Chey WD et al. Am J Gastroenterol 2017; 112:212–238

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Refractory *H. pylori*

- Previously much more common worldwide than the U.S.
- BUT
  - Overexposure to macrolides have increased background resistance of clarithromycin to *H. pylori*
  - Underuse or bismuth-based regimens and failure to confirm eradication also leads to “reinfections”

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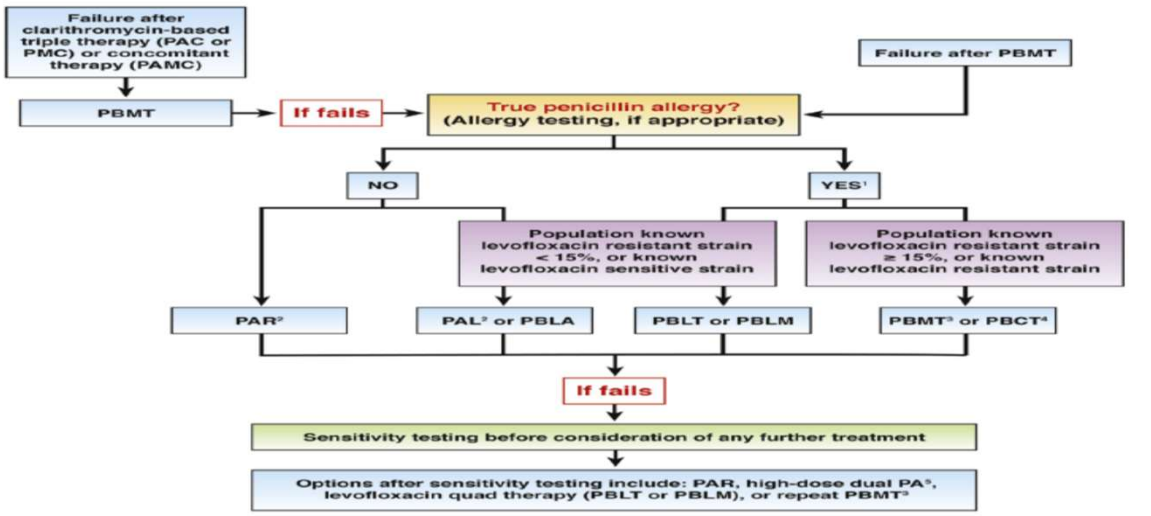

Shah SC, et al. Gastroenterology. 2021;160:1831-1841.

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H. pylori Treatment Regimens

- DO NOT SUBSTITUTE ampicillin for amoxicillin
- Consider using stool antigen after treatment to determine eradication
- Only test if you intend to treat
  - WHO? (2017 Guidelines)
    - Current PUD
    - Past PUD without known eradication
    - Certain gastric cancers
    - Unexplained iron deficiency anemia
    - Long term NSAID use (ASA, too?)

Chey WD et al. Am J Gastroenterol 2017; 112:212–238

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And (oh yeah) NSAID Use

- Recent guidelines from multiple Asia/Pacific medical societies do a superb job reviewing the literature concerning long-term use of these medications (worth the read)

Cheuk-Chun S, et al. Gut 2020, 69: 617-29.

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Avoid Long Term NSAID Use in:

- Treatment-resistant hypertension (> 3 drugs)
- High cardiovascular risk (recent MI/CVA or history of multiple CV events)
- Patients with severe CKD (eGFR <30 mL/min/1.73 m_2), or patients with moderate CKD (eGFR 30–59 mL/min/1.73 m_2) receiving ACE inhibitors, ARBs, or diuretic agents
- Routine BP and renal function checks on patients receiving long term NSAIDS is essential and often overlooked

Cheuk-Chun S, et al. Gut 2020, 69: 617-29.

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Agent Selection

- PPIs should really be considered in any patient over age 60 requiring NSAIDS OR if on DAPT or Anticoagulation OR has a history of PUD
- Celecoxib CV safety is uncertain but recent data suggests its as "safe" as naproxen

(C) Choice of NSAID and concomitant therapy

- ► high cardiovascular risk and NSAID use cannot be avoided: consider naproxen or celecoxib
- ► pre-existing hypertension and receiving ACE inhibitors or ARBs: empirical addition (or increase in the dosage) of an anti-hypertensive agent of a different class
- ► NSAID-related dyspepsia: PPI
- ► moderate risk of peptic ulcer disease: non-selective NSAID plus PPI or selective COX-2 inhibitor monotherapy
- ► high risk of peptic ulcer disease: selective COX-2 inhibitor plus PPI
- ► unexplained iron-deficiency anaemia and NSAID use cannot be avoided: consider celecoxib

Cheuk-Chun S, et al. Gut 2020, 69: 617-29.

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Role of the Pharmacy Team

- Recognize that *H. pylori* treatment failures are increasingly common in the U.S.
- Expect to see more bismuth-based quadruple therapy
  - Adherence?
- Encourage patients to follow-up with their prescribers about ensuring eradication (especially PCPs)
- Assess proper use of NSAIDs and remember the CV, renal, and GI adverse effects of this class of drug

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Gamechanger #7

The "Nocebo" Effect: Statins and Tolerability

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What is the "Nocebo" effect

- Nocebo = "I will Harm"
- The nocebo effect, the inverse of the placebo effect, is a well-established phenomenon, referring to nonpharmacological, harmful, or undesirable effects occurring after active or inactive therapy
- The frequency of adverse events can dramatically increase by informing patients about the possible side effects of the treatment, and by negative expectations on the part of the patient
  - "I've seen a lot of patients have this problem"
  - "You can expect these side effects"
- A negative effect based on the patient's expectations
- Suspected when unblinded studies of a drug have a higher ADRs rate vs. blinded studies

Chamsi-Pasha M, et al.. Avicenna J Med. 2017;7:139-143

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Statin ADRs and the Nocebo effect

- Statin-associated muscle symptoms (SAMS), is common and it is a difficult-to-manage condition.
- Some reports suggest that up to 25% of eligible patients do not take statins or have a statin "allergy" on their charts because of SAMS.
- A recent analysis of The Anglo-Scandinavian Cardiac Outcomes Trial population showed that fewer patients report SAMS with statins if they receive the drug blindly than if they receive it as an open label. Or they might have SAMS even if they received a placebo, indicating a highly improbable pharmacological basis and possible contribution of nocebo effect.
- Thus, patients who are told to expect muscle based adverse effects often do … but to date, this has not been studied systematically.

Gupta A et al. Lancet. 2017;389:2473–81

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SAMSON Study

- Double Blind, three-group, n-of-1 trial
  - Investigators enrolled 60 patients (mean age, 66 years; 58% men; 90% white) who had previously discontinued statins due to side effects that occurred within 2 weeks of therapy initiation of treatment
- Participants were given four bottles of atorvastatin 20 mg, four bottles of a placebo, and four empty bottles. Each bottle taken for a 1-month period according to a random sequence.
  - Via a smartphone app, participants reported daily symptom scores - which ranged from 0 (no symptoms) to 100 (the worst imaginable symptoms).
- Symptom severity
  - Overall, the mean reported symptom severity scores were:
    - 8 for no treatment (95% CI, 4.7-11.3);
    - **15.4** for placebo (95% CI, 12.1-18.7); and
    - **16.3** for statin therapy (95% CI, 13-19.6)

ND (p = 0.38) between placebo and drug. Thus, the Nocebo effect accounted for most (about 90%) of muscle symptom ADRs

Wood FA, et al. N Engl J Med 2020; 383:2182-2184

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SAMSON Study

- After 6 months, investigators explained the results of the trial and the implications of the nocebo effect to study subjects
  - They DID NOT tell them it was all in their heads - that they expected, perhaps subconsciously, to get the adverse effects and so they did
- Afterword, these 30 patients agreed to restart statins and ALL the patients TOLERATED THE DRUG
- What does this mean?
  - Nocebo effect is real and responsible for a lot of the complaints of SAMS
  - Taking just a few moments to explain this study could mean the difference of your patients being successfully started on these drugs
  - Work with pharmacy teams on "ADR" message?

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Bottom Line

- Many patients previously thought to not tolerate statins probably can
- Honest conversations are key
  - Highlight benefits and the rarity of serious ADRs
- Few other drugs for the cost can decrease CV death, MI, PAD, and Stroke outcomes so significantly as statins

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Gamechanger #8

Inpatient GI Bleed treatment update

Stop the (PPI Drip) Madness!

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Gastrointestinal Bleeding (GIB)

- GI varices represent a complex collection of vascular shunts between the portosplenic venous system and the systemic veins of the abdomen and thorax.
- The prevalence of GV is estimated between 17% and 25% in patients with portal hypertension and esophageal varices (EV) which are present in up to 85% of these patients.
- Bleeding rates of 16-65% are associated with mortality in CLD patients.
- Although mortality is lower in non-variceal UGIB, it is the most common GI diagnosis necessitating hospitalization in the United States - accounting for over half a million admissions annually.
- Nearly 80% of patients visiting emergency departments for UGIB are admitted to the hospital with that principal diagnosis.
- Although endoscopic treatment is the mainstay of both conditions, what is the role of medical therapy?

Peery AF, et al. Gastroenterology 2019;156:254–72.e11
García-Tsao G, et al. Hepatology 2017; 65:310–335.

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Variceal Bleeding Guidelines: AGA Update 2021

- Expert based consensus using systematic review and meta-analysis to answer direct questions.
- Does not go into detail about system used to assess or grade evidence.
- Does note that there are few large RCTs to guide therapy.
- Access to all the results of the meta-analysis as supplementary material.
- Largely a technical document - much information on endoscopic approaches to treatment, need for IR/Surgery.

Peery AF, et al. Gastroenterology 2019;156:254–72.e11
Garcia-Tsao G, et al. Hepatology 2017; 65:310–335.

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Table 2. Evidenced-Based Algorithm for Initial Management of Suspected Portal Hypertensive Bleeding

Assess circulatory status[3,21,22]	Ensure adequate vascular access (2 large-bore peripheral intravenous cannulae or central venous access) and provide fluid resuscitation (colloid or crystalloid).
Assess respiratory status[19,22]	Tracheal intubation advised for active hematemesis, inability to maintain or protect airway, and as needed to provide optimal sedation to complete endoscopic examination and therapy.
Vasoactive drug administration[3,23–25]	• Administration associated with reduced mortality and transfusion requirements. • Octreotide (somatostatin analog) initial intravenous bolus of 50 μg (can be repeated in first hour if ongoing bleeding). • Continuous intravenous infusion of octreotide 50 μg/h for 2–5 d (may stop after definitive hemostasis achieved). • Somatostatin analogs inhibit gastric acid secretion (co-administration of proton pump inhibitor not required).
Antibiotic prophylaxis[26]	• Prophylactic antibiotics reduce infections, rebleeding, and mortality. • Intravenous ceftriaxone 1 g/24 h (maximal duration 7 d).
Restrictive red blood cell transfusion[3,27]	• Transfuse at Hgb threshold of 7 mg/dL and goal maintenance Hgb of 7–9 mg/dL. • Restrictive transfusion associated with favorable effect on hepatic venous pressure gradient, decreased mortality, and decreased rate for early rebleeding.
Evaluate coagulation parameters[3,28]	• GV bleeding is precipitated by portal hypertension rather than a bleeding diathesis. Measuring and characterizing the hemostatic profile in cirrhosis is complex and high-quality data to guide practice are limited. • Overuse of blood products in cirrhosis carries significant risk, including precipitation of portal venous thrombosis. • Owing to conflicting data in the literature, there is no data-driven specific international normalized ratio or platelet cutoff in which procedural bleeding risk is reliably increased; therefore, specific transfusion cutoffs cannot be recommended. • Although low fibrinogen levels have been associated with increased bleeding risk in critically ill patients with cirrhosis, a specific threshold for transfusion has not been clinically validated. Cryoprecipitate and fibrinogen factor replacements are low-volume products effective at increasing fibrinogen levels, but a specific recommendation for transfusing these products cannot be made at this time.

PPIs NOT NEEDED IF OCTREOTIDE USED

INRs MEAN NOTHING!! CONSIDER GETTING A FIBRINOGEN AND USING CRYOPRECIPITATE IF LOW

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Non-Variceal UGIB Guidelines: ACG Update 2021

- Expert panel using PICO format and GRADE methodology to answer pertinent focused questions related to management of an acute UGIB episode and framed each question in the PICO (population, intervention, comparator, and outcome) format.
- Also did a systematic review for each PICO.
- Much less technically focused than the AGA paper (less info on endoscopic approach to UGIB for example).
- Also contains results of systematic reviews in supplementary form.
- Probably overall the more evidence-based document.

Peery AF, et al. Gastroenterology 2019;156:254–72.e11
Garcia-Tsao G, et al. Hepatology 2017; 65:310–335.

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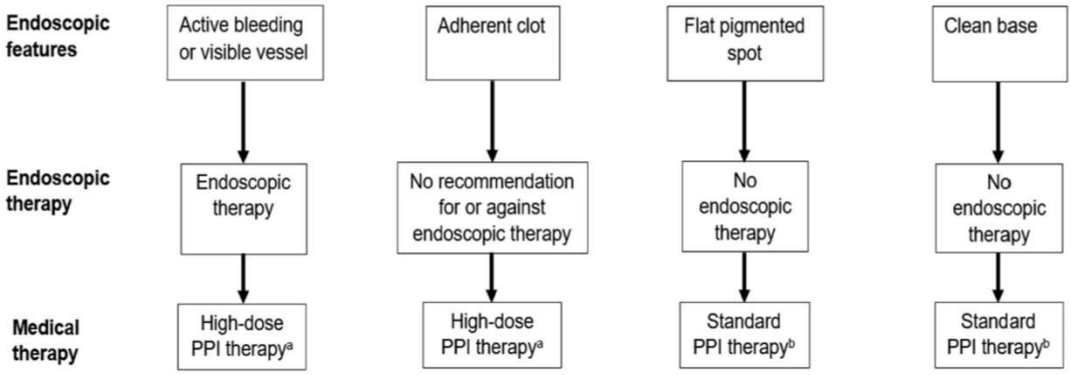

Figure 3. Endoscopic and medical therapy for ulcer bleeding based on endoscopic features of ulcer. [a]For continuous regimen, 80-mg bolus followed by 8-mg/min infusion for 3 days is recommended. For intermittent regimens, doses of 40 mg 2 to 4 times daily for 3 days are suggested, given orally if feasible, and an initial bolus of 80 mg may be appropriate. [b]Standard PPI therapy (e.g., oral PPI once-daily) has been recommended by previous guidelines (1,37) but is not assessed in the current document. PPI, proton pump inhibitor.

- HIGH dose defined as continuous **<u>OR INTERMITTENT (≥ 80 mg/day) PPI</u>**
  - ORAL is reasonable
- Standard dose defined as ONCE DAILY PPI

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WHY? - Meta analysis of RCTS found no difference in re-bleeding or mortality

Certainty Assessment								Summary of Findings				Comments
								Outcome		Effect		
Studies	Study limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality of Evidence	Overall certainty of evidence	Bolus/ contin-uous	Other regime	Relative (95% CI)	Absolute (95% CI)	
urther bleeding												
RMA of 12 RCTs[1-12]	Serious [b]	Not serious	Not serious [c]	Serious [d]	None	⊕⊕⊖⊖ LOW				RR=1.12 (0.86-1.47)	1% (-2 to 4 %)	
	Subgroup Analysis	Comparator regimen: cumulative dose ≤ 120mg/72 h [1-4]								RR=0.97 (0.63-1.49)	0% (-4 to 3%)	Subgroup difference: p=0.37; I²=0%
		Comparator regimen: cumulative dose > 120mg/72 h [1-12]								RR=1.25 (0.89-1.76)	3% (-1 to 7%)	
	Subgroup Analysis	Comparator regimen: intravenous continuous infusion, 40mg bolus and 4mg/hr infusion [9]								RR=1.29 (0.79-2.08)	7% (-7 to 21%)	Subgroup difference: p=0.54; I²=0% (Only 1 RCT (with 24% of weight) had continuous-infusion comparator)
		Comparator regimen: intermittent oral or intravenous doses, mean 40-173mg daily [1-8, 10-12]								RR=1.07 (0.78-1.48)	1% (-2 to 3%)	
	Subgroup Analysis	Comparator regimen: intermittent oral, mean 40-160mg daily [4,5,8,12]								RR=1.11 (0.57-2.16)	1% (-4 to 5%)	Subgroup difference: p=0.91; I²=0%
		Comparator regimen: intermittent intravenous, mean 40-173mg daily [1-3, 6, 7, 10, 11]								RR=1.06 (0.78-1.48)	1% (-3 to 4%)	
Mortality												
RMA of 11 RCTs[1-11]	Serious [e]	Not serious	Not serious [f]	Very serious [g]	None	⊕⊖⊖⊖ VERY LOW				RR=0.94 (0.46-1.90)	0% (-2 to 1%)	
	Subgroup Analysis	Comparator regimen: cumulative dose ≤ 120mg/72 h [1-4]								RR=0.90 (0.37-2.20)	0% (-2 to 2%)	Subgroup difference: p=0.89, I²=0
		Comparator regimen: cumulative dose > 120mg/72 h [1-11]								RR=1.00 (0.32-3.17)	0% (-2 to 2%)	
	Subgroup Analysis	Comparator regimen: intravenous continuous infusion [9]					⊕⊕⊖⊖ LOW			RR=1.00 (0.42-2.39)	-1% (-8 to 6%)	Subgroup difference: p=0.77; I²=0% (Only 1 RCT (with 11% of weight) had continuous-infusion comparator)
		Comparator regimen: intermittent oral or intravenous doses [1-8, 10, 11]								RR=1.08 (0.50-2.30)	0% (-1 to 1%)	
	Subgroup Analysis	Comparator regimen: intermittent oral [4, 5, 8]								RR=0.35 (0.01-8.30)	-1% (-5 to 3%)	Subgroup difference: p=0.49; I²=0%

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Bottom Line

- Variceal bleeding:
  - Octreotide has been shown to decrease bleeding and perhaps mortality and is an important adjunctive agent
    - WATCH OUT FOR BRADYCARDIA!
  - PPIs are not needed - at most, once daily therapy would be all that is needed (grudgingly…)
  - Don't check INRs - if continued bleeding check fibrinogen
  - DON'T use Vitamin K or FFP - consider Cryo
- Non-variceal UGIB
  - Drips have NOT been shown to be superior to intermittent dosing of PPIs to improve outcomes
  - Save money and ADRs: Just use 40 mg Pantoprazole IV BID

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Gamechanger #9

Are probiotics beneficial in patients who are critically ill?

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Probiotics and the Gut Microbiome

- More and more evidence shows that the gut microbiome plays a key role in inflammatory reactions and perhaps protection against bacterial infections throughout the body
- Probiotics have emerged as a potential way treat or prevent a wide range of infectious, inflammatory, and autoimmune conditions
  - Enhanced gut barrier function
  - Competitive inhibition of pathogenic bacteria
  - Modulation of the host inflammatory response

Johnstone J, et al. JAMA. 2021 Sep 21;326(11):1024-1033.

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Probiotics in ICU Patients

- Small randomized trials and cohort studies suggest that probiotics reduce infection rates by 20% and may decrease the risk of ventilator-associated pneumonia (VAP) by 25% to 30%
- Current guidelines suggest probiotic use for selected medical and surgical intensive care unit (ICU) patients for whom trials have documented safety and benefit
- However, does broad application of probiotics in the ICU population help? Are ADRs (particularly infections in often immunocompromised patients) an issue?
- This study examined Lactobacillus rhamnosus GG compared with placebo reduced VAP and other clinically important outcomes for a broad range of critically ill patients.

Johnstone J, et al. JAMA. 2021 Sep 21;326(11):1024-1033.

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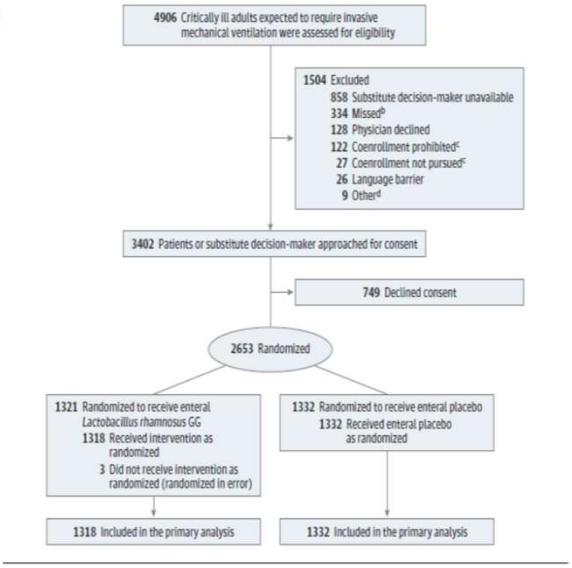
The Study:

- Mostly conducted in Canadian ICUs (Some American and Saudi as well)
- Inclusion: 18 years old, expected to require mechanical ventilation for at least 72 hours
- Exclusions:
  - already received mechanical ventilation for more than 72 hours
  - were immunocompromised
    - HIV with a CD4 cell count <200 cells/μL)
    - chronic immunosuppressive medications
    - chemotherapy in the last 3 months
    - prior organ or hematological transplant
    - absolute neutrophil count < 500 cells/μL)
  - carried increased risk of endovascular infection
  - had severe acute pancreatitis
  - had a percutaneous enteral feeding tube
  - were unable to receive enteral medication

Figure 1. Screening, Selection, and Flow of Patients in PROSPECT[a]



Johnstone J, et al. JAMA. 2021 Sep 21;326(11):1024-1033.

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Intervention

- Patients received:
  - 1 × 1010 colony forming units of L rhamnosus GG (i-Health Inc)
  - an identical enteral placebo solution (microcrystalline cellulose) twice daily for up to 60 days or until ICU discharge or if Lactobacillus species was isolated from a sterile site or cultured as the sole or predominant organism from a nonsterile site

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Outcomes

- Primary end point was VAP - presence of a new, progressive, or persistent radiographic infiltrate on chest radiograph after at least 2 days of mechanical ventilation, plus fever, leukocytosis/leukopenia or purulent sputum
  - Early VAP (pneumonia 3-5 days after initiation of mechanical ventilation) was distinguished from late VAP (after ≥ 6 days of mechanical ventilation)
- Secondary end points
  - C difficile and a composite of all ICU infections as well as presence of diarrhea
  - ADRS: Lactobacillus infections
- Stats
  - Cox proportional hazards, complex stats
  - Power: needed 2650 patients to detect a 25% relative risk reduction in VAP

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Outcomes

- No differences:
  - VAP or other infection
  - Incidence of diarrhea
  - Early or late infection
  - Antibiotic associated diarrhea

Table 2. Primary and Secondary Outcomes[a]

	No. (%) of patients				
	Lactobacillus rhamnosus GG (n = 1318)	Placebo (n = 1332)	Absolute difference (95% CI), %[b]	Hazard ratio (95% CI)	*P* value
Primary outcome					
Ventilator-associated pneumonia at any time[18,20]	289 (21.9)	284 (21.3)	0.6 (-2.5 to 3.7)	1.03 (0.87 to 1.22)	.73
Secondary outcomes					
Pneumonia					
Early ventilator-associated pneumonia[c]	50 (3.8)	61 (4.6)	-0.8 (-2.3 to 0.7)	0.80 (0.55 to 1.17)	.26
Late ventilator-associated pneumonia[d]	243 (18.4)	231 (17.3)	1.1 (-1.8 to 4.0)	1.09 (0.91 to 1.32)	.35
Postextubation pneumonia[e]	22 (1.7)	20 (1.5)	0.2 (-0.8 to 1.1)	1.21 (0.63 to 2.32)	.58
Any pneumonia[f]	307 (23.3)	300 (22.5)	0.8 (-2.4 to 4.0)	1.04 (0.89 to 1.23)	.61
Other infections					
Any infection[g]	414 (31.4)	418 (31.4)	0.0 (-3.5 to 3.6)	0.97 (0.84 to 1.11)	.64
Positive urine culture	171 (13.0)	174 (13.1)	-0.1 (-2.7 to 2.5)	0.99 (0.79 to 1.24)	.96
Any bacteremia	106 (8.0)	101 (7.6)	0.5 (-1.6 to 2.5)	1.08 (0.82 to 1.44)	.58
Skin or soft-tissue infection, nonsurgical	37 (2.8)	28 (2.1)	0.7 (-0.5 to 1.9)	1.11 (0.67 to 1.85)	.68
Any *Clostridioides difficile* infection[h]	32 (2.4)	28 (2.1)	0.3 (-0.8 to 1.5)	1.15 (0.69 to 1.93)	.60
Other infections[i]	28 (2.1)	37 (2.8)	-0.7 (-1.8 to 0.5)	0.74 (0.45 to 1.22)	.24
Skin or soft-tissue infection, surgical site	28 (2.1)	33 (2.5)	-0.4 (-1.5 to 0.8)	0.80 (0.46 to 1.39)	.43
Intra-abdominal infection	19 (1.4)	22 (1.7)	-0.2 (-1.2 to 0.7)	0.79 (0.41 to 1.50)	.47
Upper urinary tract infection[j]	2 (0.2)	3 (0.2)	-0.1 (-0.4 to 0.3)	1.02 (0.14 to 7.26)	.98
Diarrhea					
≥ 3 Stools per d	861 (65.3)	855 (64.2)	1.1 (-2.5 to 4.8)	1.01 (0.91 to 1.11)	.90
≥1 Stools of Bristol type 6 or 7[k]	1076 (81.6)	1080 (81.1)	0.6 (-2.4 to 3.5)	1.07 (0.98 to 1.17)	.13
≥3 Bristol type 6 or 7 stools per d[k]	756 (57.4)	731 (54.9)	2.5 (-1.3 to 6.3)	1.02 (0.92 to 1.14)	.66
Antibiotic-associated diarrhea					

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ADRs

- 15 infections of lactobacillus (same subtype as probiotic)
- Compared to 1 in placebo (different type of lactobacillus)
- No other major ADRs

Table 3. Adverse and Serious Adverse Events

	No. (%)		
	Lactobacillus rhamnosus GG (n = 1318)	Placebo (n = 1332)	Odds ratio (95% CI)
Adverse events[a]	13 (1.0)	1 (0.1)	
Serious adverse events[b]	2 (0.2)	0	
Serious adverse events or adverse events	15 (1.1)	1 (0.1)	14.02 (1.79-109.58)

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Conclusions and Summary

- The largest RCT ever done on probiotics in the ICU found no benefit and the potential for harm
- WHY?
  - Right dose/type of probiotic?
  - Beneficial effects of probiotics take time?
  - Other reasons?
- Bottom Line:
  - Probiotics should not be used in the ICU for most patients

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Conclusions

- Information overload!
- Focus on:
  - Areas that impact your practice
  - Variations that may change these recommendations
  - The "bottom line" slides
- PLEASE give us feedback for Gamechangers: 2023

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QUESTIONS?

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Gamechangers Podcast

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