Dabigatran: Unique Dosing Situations

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September 16, 2011

The speaker has no conflict of interest to disclose.

Objectives

- Identify appropriate patients for dabigatran therapy
- Outline a strategy to convert between dabigatran and warfarin therapy
- Identify appropriate strategies for initiation and cessation of dabigatran therapy

Mechanism of Action and Indication

- Dabigatran is an oral competitive and reversible direct thrombin inhibitor
  - Binds to both free and clot-bound thrombin
  - Inhibitory effect on tissue factor-induced platelet aggregation
- FDA approved indication: prevention of stroke or systemic embolism in patients with non-valvular atrial fibrillation (AF)

Dabigatran (Pradaxa®) Prescribing information. Ridgefield, CT, BI Pharm, Inc. 2011

RE-LY: Clinical Efficacy

18,113 patients with AF documented on ECG screening or within 6 months before enrollment and at least 1 of the following:

- Previous stroke or TIA, or systemic embolism
- LVEF <40%
- NYHA class II or higher, symptomatic heart failure
- 75 y/o *or* 65-74 y/o plus DM, HTN, or CAD

Median follow-up: 2 yrs

Open-Label

Blinded

Warfarin (INR=2-3) n= 6022	Dabigatran 110mg po BID n= 6015	Dabigatran 150mg po BID n= 6076

Primary Endpoint: stroke or systemic embolism
Safety Endpoint: Major bleeding

Connolly SJ et al. NEJM 2009;361:1139-51.

RE-LY: Main Findings

	D 110mg BID	D 150mg BID	Warfarin	D 110mg vs warfarin		D 150mg vs warfarin	
	Annual rate (%)	Annual rate (%)	Annual rate (%)	RR 95% CI	*P*	R 95% CI	*P*
Stroke or systemic embolism	1.53	1.11	1.69	0.91 0.74-1.11	0.34	0.66 0.53-0.82	<0.001
Stroke	1.44	1.01	1.57	0.92 0.74-1.13	0.41	0.64 0.51-0.81	<0.001
Hemorrhagic stroke	0.12	0.10	0.38	0.31 0.17-0.56	<0.001	0.26 0.14-0.49	<0.001
All Bleeding	14.62	16.42	18.15	0.78 0.74-0.83	<0.001	0.91 0.86-0.97	<0.002
Life-threatening bleed	1.22	1.45	1.8	0.68 0.55-0.83	<0.001	0.81 0.66-0.99	0.04
GI- Major	1.12	1.51	1.02	1.10 0.86-1.41	0.43	1.50 1.18-1.89	<0.001
Acute MI	0.72	0.74	0.53	1.35 0.98-1.87	0.07	1.38 1.00-1.91	0.048
Dyspepsia	11.8	11.3	5.8	--	<0.001	--	<0.001

Connolly SJ et al. NEJM 2009;361:1139-51.

Dabigatran: Role in Stroke Prevention

- 2011 ACCF/AHA/HRS Guideline Focused Update Recommendation: Class I, LOE B
  - Dabigatran is a useful alternative to warfarin for prevention of stroke and systemic thromboembolism in patient with paroxysmal to permanent AF and risk factors for stroke or systemic embolization
  - Those with the following are excluded: prosthetic heart valve, hemodynamically significant valvular disease, severe renal dysfunction (CrCL<15 mL/min) or advanced liver disease (impaired baseline clotting function)

Wann LS et al. Circulation. 2011 Mar 15;123(10):1144-50. Epub 2011 Feb 14.

Dabigatran: Use Criteria

- Patients taking warfarin therapy with excellent INR control may have little to gain by switching to dabigatran
- Considerations:
  - Twice-daily dosing
  - Greater risk of nonhemorrhagic side effects

Wann LS et al. Circulation. 2011 Mar 15;123(10):1144-50. Epub 2011 Feb 14.

Dabigatran: Patient Selection

- Patients who will benefit from dabigatran over warfarin:
  - AF and ≥1 additional risk factor for stroke
  - Ability to comply to twice daily dosing
  - Availability of an anticoagulation management program to sustain routine monitoring of INR
  - Patient preferences
  - Cost
  - Other factors

Wann LS et al. Circulation. 2011 Mar 15;123(10):1144-50. Epub 2011 Feb 14.

Dabigatran: Dosing

- Capsules cannot be crushed, chewed or broken
- Stability: 30 days once bottle is opened
  - Extended stability to 60 days currently under FDA review

Creatinine Clearance (CrCL)	Recommended Dosing
CrCL> 30 mL/min	150 mg orally, twice daily
CrCL 15-30 mL/min	75 mg orally, twice daily
CrCL<15 or on dialysis	Dosing recommendations cannot be provided

Dabigatran (Pradaxa®) Prescribing information. Ridgefield, CT, BI Pharm, Inc. 2011

Conversion from Dabigatran to *or* from Warfarin

Renal Function (CrCl mL/min)	Conversion Instructions: Dabigatran to Warfarin
> 50	Start warfarin 3 days before discontinuation of dabigatran
31-50	Start warfarin 2 days before discontinuation of dabigatran
15-30	Start warfarin 1 day before discontinuation of dabigatran
< 15	No recommendations can be made

Conversion from warfarin to dabigatran
• Discontinue warfarin and start dabigatran when the INR is <2

Dabigatran (Pradaxa®) Prescribing information. Ridgefield, CT, BI Pharm, Inc. 2011

Converting Dabigatran to Parenteral Anticoagulants

Agent	Conversion to Dabigatran
Heparin	Initiate dabigatran at the time heparin is discontinued
Enoxaparin	Start dabigatran at the time of the next dose of enoxaparin was to be administered (may overlap by up to 2 hours)

Renal Function CrCL (mL/min)	Converting Dabigatran to Parenteral Anticoagulants
≥ 30	Start parenteral anticoagulation 12 hours after last dabigatran dose
< 30	Start parenteral anticoagulation 24 hours after last dabigatran dose

Dabigatran (Pradaxa®) Prescribing information. Ridgefield, CT, BI Pharm, Inc. 2011

Discontinuation of Dabigatran Prior to Procedures

Renal Function CrCL (mL/min)	Half-Life (hours) Mean (range)	Timing of discontinuation after last dose of dabigatran before surgery	
		Standard Risk of Bleeding	High Risk of Bleeding
> 80	13 (11-22)	24 hours	2-4 days
> 50 to ≤80	15 (12-34)	24 hours	2-4 days
> 30 to ≤ 50	18 (13-23)	≥ 48 hours	≥ 4 days
≤ 30	27 (22-25)	48-120 hours	≥ 5 days

•Standard risk of bleeding : electrophysiology procedures, cardiac catheterizations, no additional patient-specific risk factors.

•High risk of bleeding: surgery involving major organs, procedures requiring complete hemostasis or when additional patient risk factors are present.

Adapted from: van Ryan J et al. Thromb Haemost 2010;103:1116-27.

Clinical Question

HPI/CC: 66 y/o M presents to the ED febrile and SOB resulting in hypoxemic respiratory failure requiring intubation. Chest x-ray demonstrates a LLL infiltrate. The patient is transferred to the MICU with an oral-gastric tube placed.

PMH:
Non-valvular atrial fibrillation

Medications PTA:
Dabigatran 150mg po BID
(last dose taken this morning)

Pertinent Laboratories:
Weight: 80 kg
Scr =1
CrCL= 60 mL/min
INR =1.2
aPTT= 25

The medical team would like your recommendations to initiate therapeutic anticoagulation.

Clinical Question

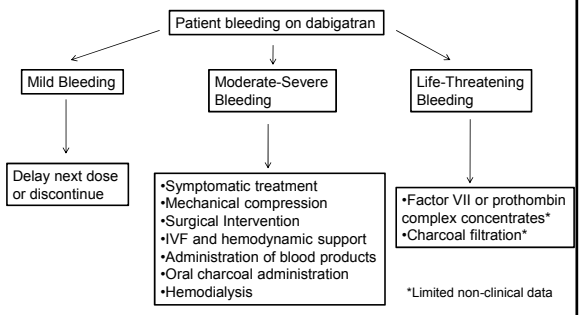
A. Initiate enoxaparin 80mg SC 24 hours after the last dabigatran dose
B. Initiate enoxaparin 80mg SC 12 hours after the last dabigatran dose
C. Initiate heparin 5000 units SC12 hours after last dabigatran dose
D. Continue dabigatran therapy and administer through the oral-gastric tube

Dabigatran Monitoring

- Dabigatran has the potential to prolong aPTT, TT, and ECT
  - aPTT targets the intrinsic pathway of the clotting cascade
    - 2-fold increase in patients treated with 150mg BID
    - Can increase to 1.5 x control 12 hours after dose;however it becomes insensitive at higher concentrations
  - TT directly measures thrombin in plasma sample
    - Linear dose-response over therapeutic concentrations and provides direct measure of activity
    - Limitations: reagents are not standardized and cut-offs cannot be defined
  - ECT specific to thrombin generation
    - Available only in research setting
- Limited data on the use of ACT
- Dabigatran should be discontinued for at least 2 days for an accurate INR
- No guidelines for routine monitoring

van Ryan J et al. Thromb Haemost 2010;103:1116-27.

Dabigatran Related Bleeding and Reversal



Adapted from: van Ryan J et al. Thromb Haemost 2010;103:1116-27.

Dabigatran and Cardioversion

- AF ≥ 48 hours or unknown duration: therapeutic anticoagulation with warfarin for at least 3 weeks before and 4 weeks after cardioversion[1]
- RE-LY Data[2]
  - Incidence of stroke and major bleeding in within 30 days were similar in both dabigatran groups compared to warfarin with or without TEE
  - Study drug administration ≥ 3 weeks
  - Role of dabigatran unclear if in AF <48 hours
  - Reasonable alternative to warfarin

1. Singer DE et al. Chest 2008;133:546s-92s.
2. Nagarakanti R et al. Circulation 2011;123:131-6.

Dabigatran and Ischemic Stroke

- Considerations with monitoring dabigatran as compared to warfarin therapy
  - INR cannot be used reliably in dabigatran treated patients
  - Limitations with reliability of aPTT, TT or ECT
- Dabigatran treated patients who present with an ischemic stroke should not be considered for t-PA
  - Potentially high risk of hemorrhage

Prabhakaran S. Arch Neurol. 2010 Sep;67(9):1156; author reply 1156-7.

Dabigatran: Special Populations

Case 1

- 84 y/o female, weight 40 kg
- Dabigatran 75mg po BID
- Treatment x 4 months
- Presents with rectal bleeding
- CrCL=32 mL/min
- TT= 5600 ng/mL (31-225 ng/mL)
- Expired from hemorrhagic shock

Case 2

- 89 y/o female, weight 45 kg
- Dabigatran 110mg po BID
- Treatment x 5 months
- Presents with recurrent epistaxis x 1 week and surgery for cochlear implant removal
- CrCL= 29 mL/min
- TT= 2670 ng/mL (31-225 ng/mL)
- Dabigatran discontinued

Legrand M et al. Arch Intern Med 2011;171:1285-88.

Considerations for Dabigatran Initiation

- Appropriate monitoring
- Compliance
- Athlerosclerotic arterial disease
- Bleeding risk / lack of reversal
- Alterations in renal function
- Obese or underweight patients
- Drug-interactions
- Available route of administration
- Insurance coverage/ cost

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ICHP Clinical Pearl
Dabigatran: Unique Dosing Situations
Jill Cwik, Pharm.D.

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Controversies surrounding creatinine clearance

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The speaker has no conflicts to disclose.

Objectives

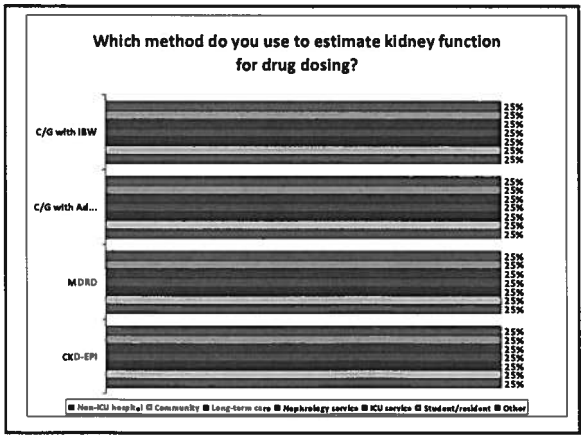
- Recognize new and traditional methods of estimating kidney function using creatinine measurement.
- Identify factors that confound creatinine-based estimation of kidney function.

What is your practice site?

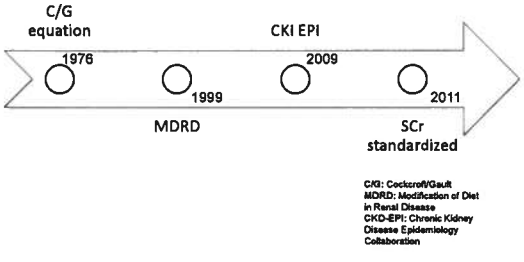
1. Non-ICU hospital
2. Community
3. Long-term care
4. Nephrology service
5. ICU service
6. Student/resident
7. Other

Which method do you use to estimate kidney function for drug dosing?

1. C/G with IBW
2. C/G with Adj BW
3. MDRD
4. CKD-EPI



Timeline



Standardization of SCr

- Isotope dilution mass spectrometry (IDMS) – standardized
- 5-20% positive bias before standardization
- Affects all SCr based assessments of kidney function
  - No universal C/G "adjustment factor"

Miller WG. Arch Pathol Lab Med. 2005;129:297-304.

After standardization of SCr, dosing medications with C/G would be expected to result in which of the following?

1. Increased dose/frequency
2. No change in dose/frequency
3. Decreased dose/frequency

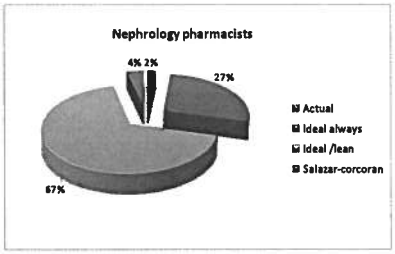
Cockcroft-Gault

- Cr_{Cl}= [((140-age) x weight)/(72 x S_{cr})] x 0.85 if female

Controversy Detector

Variations on a theme

- Weight
  - IBW
  - Adjusted
  - Total

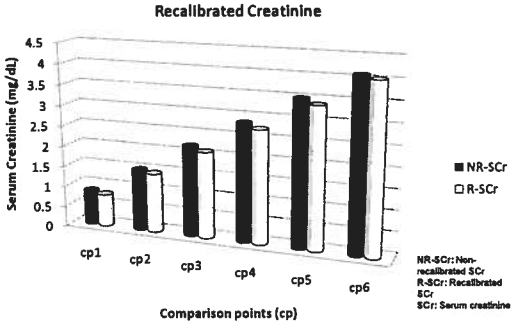


Dowling. Pharmacotherapy. 2010;30:776-86.
Wilhelm. Pharmacotherapy 2011;31:658-664.

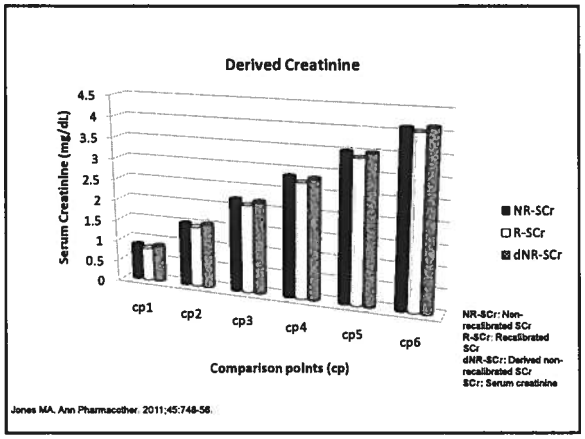
Variations on a theme

- SCr rounding in elderly
  - To 1 mg/dL
    - Likely under doses medications
  - To 0.7 mg/dL
    - Some support

Khuu. Am J Health Syst Pharm. 2010;67:274-9.
Wilhelm. Pharmacotherapy 2011;31:658–664.



Jones MA. Ann Pharmacother. 2011;45:748-56.



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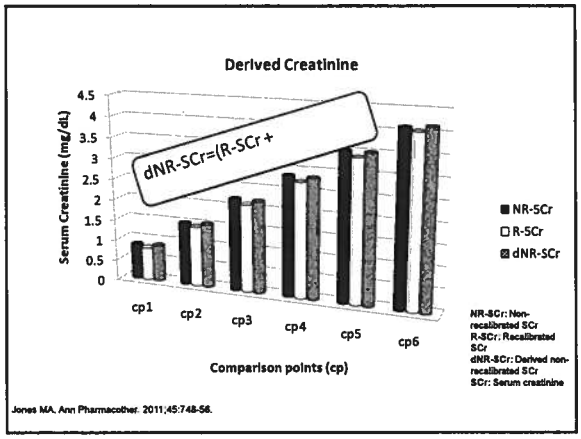


Jones MA. Ann Pharmacother. 2011;45:748-56.

MDRD

- Equations
  - 6 variable
    - eGFR = 170 x $Scr^{-0.999}$ x $age^{-0.176}$ x $BUN^{-0.170}$ x $Alb^{0.318}$ x (0.762 if female) x (1.180 if black)
  - 4 variable
    - eGFR = 186 x $Scr^{-1.154}$ x $age^{-0.203}$ x (0.742 if female) x (1.212 if African American)
    - eGFR = 175 x $SCr^{-1.154}$x $age^{-0.203}$ x (0.742 if female) x (1.212 if African American)

Levey. Ann Intern Med.1999;130:461-470.
Levey. J Am Soc Nephrol.2000;11:155A.
Levey. Ann Intern Med 2006;145:247-55.

MDRD

- Clcr < 60 mL/min
- Elderly
- BSA adjustments
- For dosing?
  - Generally MDRD results in higher estimates of GFR compared with C/G

Using MDRD to estimate GFR would be expected to result in which of the following (compared to C/G)?

1. Increased dose/frequency
2. No change in dose/frequency
3. Decreased dose/frequency

CKD-EPI

- GFR = 141 × min(Scr/κ, 1)$^{\alpha}$ × max(Scr/κ, 1)$^{-1.209}$ × 0.993^{Age} × 1.018 [if female] x 1.159 [if black]
  - κ is 0.7 for females, 0.9 for males
  - α is -0.329 for females, -0.411 for males
  - min indicates the minimum of Scr/κ or 1
  - max indicates the maximum of Scr/κ or 1
- Better than MDRD for GFR > 60 mL/min

Levey. Ann Intern Med. 2009;150:604-612.

CKD-EPI

- In one study
  - ~5 mL/min greater estimates vs C/G overall
  - ~8 mL/min greater in African Americans
- This resulted in...
  - 15-25% discordance
- MDRD resulted in...
  - 20-36% discordance

Wargo. Ann Pharmacother. 2010;44:439-46.

What do the pharmacy experts use?

- What equation do you use to adjust meds?
  - Nephrology pharmacists 96.4%
  - Critical care pharmacists 94.6%

Who are Cockcroft & Gault?

Dowling. Pharmacotherapy. 2010;30:776-86.

What do organizations recommend?

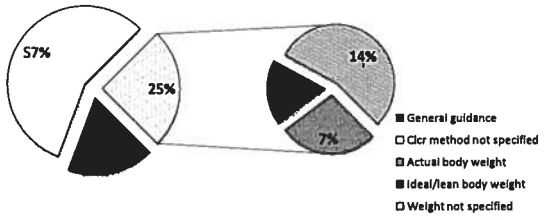
- NIDDK/NKDEP (Jan 2010 recommendation)
  - Use either C/G or MDRD
- FDA guidance to industry (Mar 2010 draft)
  - Use either C/G or MDRD

NIDDK: National Institute of Diabetes, digestive and kidney diseases
NKDEP: National Kidney Disease Education Program
FDA: Food and Drug Administration

NIDDK Chronic Kidney Disease and Drug Dosing: Information for Providers accessed from http://www.nkdep.nih.gov/professionals/drug-dosing-information.htm
FDA guidance for industry accessed from http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances

Labeling

- A review of NME's from 1998-2007 revealed:



Dowling. Pharmacotherapy. 2010;30(8):776-86.

NME: New molecular entity

Limitations of SCr

- Changing renal function
- Can reflect changes in diet/muscle mass

Which of the following is recommended in the setting of acute kidney injury?

1. C/G
2. MDRD
3. CKI-EPI
4. 24 hr urine collection

Hey, where are my pearls???

- For now
  - C/G to estimate Clcr for drug dosing
    - IBW/adjusted (unless actual used in FDA PK studies)
    - SCr: round to 0.7 mg/dL as opposed to 1 mg/dL
  - MDRD/CKD-EPI for most accurate assessment of renal function
  - For acutely changing SCr or narrow therapeutic index
    - Consider 24 hr urine collection
- Watch for revisions to guidance!

Which of the following methods of measuring kidney function is most accurate when GFR is > 60 mL/min?

1. Cockcroft/Gault
2. 4-variable standardized MDRD
3. 6-variable MDRD
4. CKD-EPI

Which of the following is currently a limitation of creatinine-based measures of kidney function?

1. Inter-laboratory variability in creatinine measurement
2. Fluctuation with muscle mass
3. Inconvenient sample collection
4. Expense

Team Scores

		○	
		○	
		○	

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Clinical Pearls - Handout
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Probiotics: The Helpful or Harmful Fungus among us?

September 16, 2011

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Speaker has no conflict of interest to disclose.

Objectives

- Explain the regulatory issues concerning probiotics
- Identify potential risks associated with probiotic use
- List patient populations in whom probiotics should be avoided

World Health Organization

Definition

Probiotics are:

"live microorganisms which when administered in adequate amounts confer a health benefit on the host."

ftp://ftp.fao.org/es/esn/food/wgreport2.pdf

Drug *versus* Dietary Supplement

Drug	Dietary Supplement
• An article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease	• A product taken by mouth that contains a "dietary ingredient" intended to supplement the diet
• Regulated by the FDA	• Regulated by the FDA's Center for Food Safety and Applied Nutrition
• Requires FDA approval prior to marketing	• Does NOT require FDA approval prior to marketing
Required to record and forward to FDA any reports of serious adverse effects	

Venugopalan V, et al. *Emerg Infect Dis* 2010;16:1661-65.
Heimbach JT. *Clin Infect Dis* 2008;46:S122-4.

Structure/Function *versus* Health Claims

Structure/Function	Health
• FDA requires that manufacturers' substantiations of claims are to be supported/accepted by experts in the field	• Describe "a relationship between a food, food component, or dietary supplement ingredient, and reducing risk of a disease or health-related condition"
• Claim is truthful and not misleading	• Require a petition containing the scientific evidence supporting the claim to be submitted to the FDA
• Data do not have to be made publically available and do not need to be disclosed	• Only data from those studies in healthy populations are evaluated
• Manufacturers must state, "the FDA has not evaluated the claim and the product is not intended to diagnose, treat, cure, or prevent any disease"	• Data must be published

Venugopalan V, et al. *Emerg Infect Dis* 2010;16:1661-65.
Heimbach JT. *Clin Infect Dis* 2008;46:S122-4.

Probiotic Evaluation Standards

Guideline Recommendations

- Identification of the genus and species of the probiotic strain
- *In vitro* testing to validate the mechanism of effect
- Substantiation of clinical health benefit with human trials
- Safety assessment
- Manufacturers responsibility to ensure that an independent third party reviews and evaluates all scientific evidence

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Probiotic Claims

- Marketed as dietary supplements
  - *Saccharomyces boulardii*
  - *Lactobacillus* species
  - *Bifidobacterium* species
- Structure/function claims on packaging
  - Promotes intestinal health
  - Keeps intestines functioning well
  - Maintains balance of intestinal flora and protects intestinal tract

Helpful?

- Proposed mechanisms
  - Lower intestinal pH
  - Modifying the host immune response
  - Decrease colonization and invasion by pathogenic organisms
  - Protease production that decreases toxicity of *C. difficile* toxins
- Many disease states studied
  - e.g., prevention of antibiotic-associated diarrhea (AAD) and treatment of *Clostridium difficile* infection (CDI)

Shanahan, F. *Gastroenterol* 2010;139:1808-12.

Meta-analysis (# of studies included)	Conclusion	Limitations
Tung, JM, *et al. Can J Gastroenterol* 2009;23:817-821. (4)	*Saccharomyces boulardii* is well tolerated and may be effective for secondary prevention in specific patient populations with particular antimicrobial concomitant therapy. Primary prevention needs further study.	• Small sample sizes not powered to detect statistically significant differences • Variability of antimicrobials used • Short follow-up
Pillai A, *et al. Cochran Database Syst Rev* 2008;1:CD004611 (4)	Insufficient evidence to recommend probiotics as an alternative or adjunct to antimicrobial therapy for CDI	• Small samples sizes • Considerable heterogeneity related to antimicrobial use and initial disease • No random assignment of antimicrobials • No standardization of probiotics
McFarland, LV. *Am J Gastroenterol* 2006;101:812-822. (25)	Variety of probiotics are promising effective strategies for antibiotic-associated diarrhea and CDI; *Saccharomyces* effective for CDI	• Prevention and treatment studies combined • Pooled odds ratio driven by single positive study • AAD conclusions applied to both pediatric and adults • Variety of probiotics evaluated • Five studies included *H. pylori* infection
Dendukuri N, *et al. CMAJ* 2005;173:167-170. (8)	Insufficient evidence to recommend probiotics for the treatment or prevention of CDI	• Small sample sizes • Short duration of follow-up in majority of studies • No standardization of probiotics or probiotic doses
RD'Souza, AL, *et al. BMJ* 2002;324:1361. (9)	Probiotics may be used to prevent AAD however, insufficient evidence to recommend probiotics for treatment.	• Variety of concomitant antimicrobials used • Variety of probiotics compared

Helpful Yogurt?

- Randomized, double-blind, placebo-controlled study (N = 135)
- Objective: To determine the efficacy of a *Lactobacillus* drink for the prevention of AAD and CDI
- 97ml yogurt drink Q12h during antimicrobial treatment and for one week after cessation of antimicrobial; placebo group received sterile milkshake
- Exclusion criteria: diarrhea on admission, bowel pathology that may result in diarrhea, antimicrobial use in previous 4 weeks, severe illness, immunosuppression, bowl surgery, artificial heart valves, history of rheumatic disease or endocarditis

Hickson, M, et al. BMJ 2007;335:80-83.

Helpful Yogurt?

Treatment group	AAD N (%)	Absolute Risk Reduction	Number Needed to Treat	CDI N (%)	Absolute Risk Reduction	Number Needed to Treat
Probiotic drink (N = 57)	7 (12%)	21.6% (6.6-36.6%)	5 (3-15)	0	17% (7-27%)	6 (4-14)
Placebo (N = 56)	19 (34%)			9 (17%)		
	p = 0.007			p = 0.001		

Conclusion: Probiotics may reduce the incidence of AAD and CDI.
"Potential to decrease morbidity, healthcare costs, and mortality if used routinely in patients aged over 50."

Hickson, M, et al. BMJ 2007;335:80-83.

Helpful Yogurt?

- Limitations:
  - Patients taking high risk or more than 2 recent courses of antimicrobials were excluded
  - Products were in different containers (thus, not blinded)
  - Placebo group received milk product which may have contributed to diarrhea (may have led to CDI testing)
  - Not clear if subjects in each group were screened equally when diarrhea occurred

Hickson, M, et al. BMJ 2007;335:80-83.

Or Harmful?

- Risk Associated with Probiotic Use
  - "Well tolerated, minimal adverse effects"
  - Package insert lists gas, constipation, and thirst

> "If you have a central venous catheter, please speak with your health care professional before you start taking *Saccharomyces boulardii*. Very rare cases of fungemia have been observed in patients with a central venous catheter. In all cases the course was favorable after antifungal treatment."

Florastor®[package insert]. San Bruno, CA: Biocodex, Inc.

Harmful?

- *Saccharomyces* fungemia is the most severe complication
- *S. cerevisiae* and *boulardii* used interchangeably as they are genetically similar and share metabolic properties

Mackenzie DA, *et al. Yeast* 2008;25:501-512.

Harmful?

- 91 documented cases of invasive *Saccharomyces* infections
  - 54 *S. cerevisiae* invasive infections
  - 37 cases of *S. boulardii* fungemia

	S. boulardii	***S. cerevisiae***	***p*-value**
Digestive tract disease	58%	6%	$p < 0.01$
Intravenous catheters	83%	29%	$p < 0.0001$
Intensive care unit admission	32%	0.05%	$p < 0.01$

40% of all cases were associated with *S. boulardii* use

Enache-Angoulvant A, *et al. Clin Infect Dis* 2005;41:1559-68.

Harmful?

60 cases of *S. cerevisiae* fungemia

Patient Characteristics	Percent
Received *S. boulardii* probiotic preparation	48
Housed near patients receiving *S. boulardii*	9
Admission in the Intensive Care Unit	60
Receiving enteral or parenteral nutrition	71
Central venous catheter present	93
Received broad spectrum antimicrobials	88
Fungemia detected a median of 10 ± 62.3 days (range 4-300) after probiotic administration	

28% Mortality Rate

Muñoz P, *et al. Clin Infect Dis* 2005;40:1625-34.

Harmful?

Hennequin *et al.*

- Air and surface contamination evaluated before, during, and after opening a *Saccharomyces* capsule
  - Massive air contamination that persisted for 30 minutes
  - Persisted up to 2 hours on the table surfaces
  - Remained on the arm of a simulated patient for 30 minutes

Hennequin C, *et al. Eur J Clin Microbiol Infect Dis* 2000;19:16-20.

Harmful?

Hennequin *et al.*

- Hand contamination on the technician who prepared the dose was evaluated
  - Gloves were not worn
  - Hands tested prior to preparation and after vigorous hand washing
  - Hands remained highly and persistently contaminated despite vigorous handwashing

Hennequin C, *et al. Eur J Clin Microbiol Infect Dis* 2000;19:16-20.

2010 CDI Guidelines

"Administration of currently available probiotics is not recommended to prevent primary CDI, as there are limited data to support this approach and there is a potential risk of bloodstream infection."

Cohen SH, *et al. Infect Control Hosp Epidemiol* 2010;31:431-55.

Patient Populations to Avoid Probiotics

- Immunocompromised patients
- Critically ill patients located in an intensive care unit
- Patients with central venous access or other lines/ports, etc.

Other Considerations

- Discrepancies in content
  - Doron and Gorbach evaluated 18 commercially-available probiotic products
    - 39% had discrepancies between actual concentrations and what the label claimed
  - Sargent *et al*. evaluated Brewer's Yeast tablets
    - No viable yeast identified
  - Masco and colleagues evaluated 58 bifidobacteria-containing products
    - 29% contained no bifidobacteria

Doron S, *et al. Expert Rev Antiinfect Ther* 2006;4:261-75.
Sargent G, *et al. The Pharmaceutical Journal* 2004;273:230-1.
Masco L, *et al. Int J Food Microbiol* 2005;102:221-30.

In Summary…

- Probiotics are dietary supplements
  - Only eligible for health claims *versus* drug claims
- Fungemia is a serious risk associated with probiotic use
- Avoid probiotics in immunocompromised or critically ill patients, patients with IV access

Post-Test Assessment

- Which one of the following claims is appropriate for probiotics?

A. Prevents *Clostridium difficile* infection
B. May be used as an adjunct to CDI treatment
C. Treats *Clostridium difficile* infection
D. Maintains balance of intestinal flora

Post-Test Assessment

- Which one of the following patients would probiotics be considered a possible option to prevent AAD and CDI?

A. 89 yo F from a nursing home admitted to the ICU who is receiving cefepime for urosepsis
B. 47 yo M admitted to the general medicine floor who is receiving moxifloxacin for CAP
C. 60 yo F with no known health problems and a history of AAD who is initiated on antimicrobials for sinusitis in the outpatient setting
D. 72 yo F on immunosuppressants s/p liver transplant who is initiated on ciprofloxacin for a UTI in the outpatient setting