Hospital Based Probiotic Protocol

Policy
Hospital provides probiotics in food form for patients receiving antibiotics unless contraindicated. Any health professional may order or provide food based probiotics per protocol without co-signature. Probiotics administered via enteral tube or in pill form require orders by a doctor or by a dietitian with order writing privileges.

Procedures
- start probiotics within 2 days of starting antibiotics,
- separate probiotics 2 hours from oral antibiotic dose,
- continue probiotics after antibiotic course for at least 1 week and up to 4 weeks,
- see local work instructions for site specific instructions.

Indications
- Patients on antibiotics, especially those on high risk or broad spectrum antibiotics, who are at risk for developing antibiotic associated diarrhea (AAD) or *Clostridium difficile* infection (CDI)
- Patients who are at risk of ventilator associated pneumonia (VAP) or related conditions
- May be used for other evidence based indications
- May be used for per patient request unless contraindicated.

Contraindications

Absolute Contraindication:
- Milk protein allergy

Relative Contraindications:
- Neutropenic (absolute neutrophil count less than 500)
- Immunosuppressed patients (i.e. patients on high dose immunosuppressant medication)

Note: Lactose intolerance is not a contraindication for kefir or yogurt products. Lactose levels per dose of Nancy’s Kefir are low, around 2 to 3 grams, and three of the probiotic species in Nancy’s kefir actually help digest lactose and are actually indicated for the treatment of lactose intolerance.
## Probiotic Products

<table>
<thead>
<tr>
<th>Food based Probiotic Product</th>
<th>Probiotic Dose and dose options</th>
<th>Effectiveness</th>
<th>Comments</th>
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<tbody>
<tr>
<td><strong>Nancy’s Kefir, plain</strong></td>
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<tr>
<td>Mixed probiotics:</td>
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<tr>
<td>• L. Casei</td>
<td></td>
<td>(see above)</td>
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<tr>
<td>• L. rhamnosus</td>
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<td>(see above)</td>
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<tr>
<td>• L. acidophilus including LA-5®, LB3;</td>
<td>10-20 billion CFU/day:</td>
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<tr>
<td>• Bifidobacterium including BB-12*</td>
<td>45 ml (1.5 oz) qd to bid</td>
<td>42 to 57% lower hospital acquired C. difficile (CDC data on Good Samaritan, Corvallis, Oregon, 2013-2015, p&lt;0.03)</td>
<td>Eneral administration: Dilute kefir 50:50 with water, flush 30 ml water before and after.</td>
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<tr>
<td>Prebiotics: inulin, lactose</td>
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<td>Other details proprietary</td>
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| **Nancy’s Kefir, flavored**  |                                 |              |         |
| Mixed probiotics (see above)|                                 |              |         |
| Prebiotics: inulin, lactose, agave | 10-20 billion CFU/day:  |              |         |
| Other details proprietary   |                                 |              |         |

| **Nancy’s Yogurt**          |                                 |              |         |
| (see above)                 |                                 |              |         |
| [www.nancysyogurt.com](http://www.nancysyogurt.com)  | 10-20 billion CFU/day:  |              |         |
| [www.dannon.com/danactive](http://www.dannon.com/danactive)  | 120 ml (4 oz) qd to bid | 44% to 64% lower hospital acquired C. difficile (CDC data on Legacy Hospital system in Portland, Oregon, 2013, Hospital Compare SIRs 0.36-0.56, significantly better than national) | Oral or enteral. Dilute plain yogurt with water before enteral administration. Flush before and after. |
| [www.culturelle.com](http://www.culturelle.com)  | 240 ml (8 oz) qd            |              |         |

| **DanActive®**              |                                 |              |         |
| L. Casei immunitas®         | 20-40 billion CFU/day:          |              |         |
| [www.dannon.com/danactive](http://www.dannon.com/danactive)  | 3.5 oz bottle bid              | 65% lower hospital acquired C. difficile (NNT=6) Hickson et.al 2007 | Oral or enteral |
| **Generic (?) yogurt or kefir with mixed probiotics with L.Casei and/or L.Rhamnosis and a “live and active” culture seal** | At least 10 billion CFU per day 1 to 2 cartons (6oz) per day has 7.5 to 15 billion CFU per 6 ounces (3/4 cup) yogurt/kefir if it has specified species and a “Live and active culture” seal | ??? Possibly ~40% to 80% lower risk CDI per meta-analysis on mixed probiotics however using untested yogurt/kefir may or may not be effective. (Ann Intern Med 2012, Cochrane Review 2013) Combinations with only L.acidophilus and Bifidobacterium or only S.thermophilus and L.Bulgaricus were not effective. | Must have “Live and active culture” seal. Levels fall by half by end of shelf life, so 6 oz carton starts with ~15 billion and ends with ~7.5 billion. |

| **Supplement pills**        |                                 |              |         |
| **Culturelle®**             |                                 |              |         |
| L. rhamnosus GG             | 10 billion CFU/capsule:         |              |         |
| [www.culturelle.com](http://www.culturelle.com)  | 1 capsule bid for CDI prevention | 10-20 billion CFU 37% lower hospital acquired C. difficile average per meta-analysis (Ann Intern Med 2012) 20 billion bid: 69% lower hospital acquired C.diff (Morrow et al 2010) 50% lower VAP (Morrow et al 2010) | Use dairy free Culturelle® when pt has dairy allergy or needs fluid restrictions. Directions for vent pts: 1 capsule mixed in water based surgical lubricant delivered to oropharynx 1 capsule in water delivered through NG tube This is done twice a day. |
| **FloroStor®**              |                                 |              |         |
| S. Boulardii                 | 250-500 mg twice a day 1-2 capsules twice a day | 60% less risk CDI in meta-analysis (Ann Intern Med 2012) | Caution with enteral administration: Case reports of S.Boulardii (probiotic yeast spores) causing port infections when capsules opened, spores can travel ~1 meter and stay on nurses’ skin even after washing. |
| [www.florastor.com](http://www.florastor.com)  | 1-2 capsules twice a day        |              |         |
| **Bio-K® 3.5 oz probiotic dairy drink or capsule, 50 billion CFU:** | 50 billion CFU once or twice a day | 73 to 95% less risk CDI (Gao et al 2010, Maziade et al 2013) CDI<3.0 per 10,000 pt days  (Maziade et al 2013) |         |
| L. acidophilus CL1285®       | 3.5oz dairy drink qd to bid     |              |         |
| L. rhamnosus CLR2®           | 1 capsule qd to bid             |              |         |
| L. casei LBC80R®             | Notes: Gluten free             |              |         |
| [www.biokplus.com](http://www.biokplus.com)  |                              |              |         |

Some probiotics help prevent Clostridium Difficile infection and some do not. Probiotics demonstrated to be effective for prevention of Clostridium Difficile Infection are listed in the table below. Probiotics products from outside the U.S. not included. Probiotics listed are generally recognized as safe and meta-analysis has found no differences in adverse effects of probiotics versus placebo. Colony Forming Unit (CFU) dose indicated is for probiotics and does not count the starter cultures (L. bulgaricus and S. thermophiles) which may have benefits but do not colonize the human gut and are not traditionally included in probiotic count.
Sample Hospital Based Probiotic Protocol, Sara Lee Thomas, MS, RD, LD. Implemented at Good Samaritan Regional Medical Center in Corvallis, Oregon

References:

6. OHSU 2007 Probiotic protocol with Nancy’s Yogurt by Dr. Robert Martindale, shared with permission and changed, adapted and approved in 2011 for use at Good Samaritan Regional Medical Center in Corvallis, Oregon.
7. Public data from CDC compiled by Sara Lee Thomas, MS,RD, LD on Nancy’s Kefir Hospital Based Probiotic protocol. CDC direct data on Good Samaritan Regional Medical Center, Corvallis, Oregon, 2013-2015, p<0.03. VAP/VAE data from Infection prevention department is observational only and had CDC definition changes mid-way.
8. Public data from Hospital Compare/CDC compiled by Sara Lee Thomas, MS, RD,LD. The Legacy hospital system in Oregon use a probiotic protocol using Nancy’s yogurt for prevention of Antibiotic Associated Diarrhea and has achieved hospital acquired CDI rates significantly “Better than the US National Benchmark” in 2013 with a SIR of 0.56 for their level I trauma center, Legacy Emanuel, and 0.41 and 0.36 for their other two acute care hospitals.
Examples of Work instructions

Work Instruction Example 1:

**WORK INSTRUCTION STEPS:**

Standard Kefir order: 2 oz Nancy’s Kefir twice a day.

1. Per Kefir protocol, the Registered Dietitians will screen all patients receiving antibiotics. For patients that do not have kefir ordered and with no contraindications, the standard kefir order will be added per Registered Dietitian order writing privileges.
2. Nutrition Services Dietary Aide will note any patients with kefir ordered BID on the Nutrition Services sign off sheet in the EMR.
3. Nutrition Services will send kefir on each Breakfast and Dinner tray.
4. A kefir information card will be added to each tray to alert the patient that kefir is being sent.
5. If a patient is receiving a specialized diet the nutrition facts of kefir will be included in the total for that meal.
6. If the patient specifies that they prefer a kefir smoothie, Nutrition Services staff will make note of it in the EMR and send as appropriate.
7. If pt is on a liquid thickness or altered texture diet, the diet aides will modify the kefir appropriately.
8. The Dietary Aides will track all kefir sent on the Kefir Tracking Form.

Work Instruction Example 2:

**Ordering/Receiving:**

1. Kefir will be ordered by the Physician or Dietitian per Order Writing Privileges for Registered Dietitians (without co-signature) into the EMR.
2. For patients that do not have Kefir ordered the Dietitian will assess patients receiving antibiotics and the appropriateness of the Kefir per the indications and contraindications listed above.
3. For patients whose diet order is for thickened liquids, high probiotic yogurt will be provided.
4. Nursing to administer Kefir off of the nursing work list and document in the EMR as appropriate

Work Instruction Example 3:

**Oral Administration of Kefir**

- Oral Kefir may be given by nursing staff when indicated per protocol unless the patient is NPO or there is a contraindication.
- Order Kefir in the EMR “Per Protocol, no co-sign required”.
- Kefir will be available to nursing and stored in the fridge in ACU and CCU.
- Administer 60 mls of Kefir bid to the patient.
- Document administration of Kefir in the EMR under “I and O”.

**Feeding Tubes or NG Tube Administration of Kefir**

- Use plain Kefir for feeding tubes or NG tubes.
- Plain Kefir is available in CCU and ACU refrigerators.
- Do not add Kefir directly to Tube Feeding formula or into enteral feeding bags.
- Measure out 2 oz of plain Kefir.
- Mix with 2 oz of tap water.
- Flush Kefir water mixture with a syringe into feeding tubes and NG tube.
- Flush with 30 mls of water before and after administration of Kefir.
- Document administration of Kefir in the EMR under “daily cares and safety”.

**Kefir Swabs for Prevention of Ventilator Associated Pneumonia in CCU**

- Obtain “Kefir for mouth swabs” bid from provider.
- Dip the oral swab into kefir and swab the mouth for about 30-60 second after the Chlorhexidine rinse and oral care
Work Instruction Example 4 (Good Samaritan Regional Medical Center, Corvallis, OR)

PROCEDURES:

Oral Administration of Kefir

- **Kefir Floor stock**: Pre-flavored Nancy’s kefir may be kept as floor stock and nursing staff may give to patients when indicated per protocol or per patient request. 4 oz once a day or 2 oz twice a day is adequate for benefit. Unless patient is on a regular diet, amounts over 4 oz a day requires provider or dietitian order since larger amounts may impact other nutrition restrictions.
- **Kefir Orders**: May be ordered and added to meals or snacks by a LIP or Dietitian order when indicated. Options:
  - Kefir: Nancy’s flavored Kefir will be delivered twice a day with morning and afternoon snacks from nutrition services unless otherwise indicated.
  - Kefir-fruit smoothies: 3oz plain kefir added to 4 oz V8Fusion Fruit/vegetable smoothie, +/- 1 oz liquid protein (15g)

Enteral Administration of Kefir via Feeding Tube:

- Order "Kefir for TF bid" (standard) or "Kefir for TF tid". Orders will start 7am the next day unless orders called down to kitchen, ext.3663 (FOOD)
- Starting and stopping kefir via feeding tube requires a LIP order directly or via delegation to dietitian to "evaluate and treat" for tube feeding.
- Nursing staff will be responsible for administering and documenting Nancy’s Kefir through feeding tube.
- Food and Nutrition Services will print labels "Kefir for TF, deliver to nursing" with patient identifiers and deliver to nursing.

Procedure for Non-ICU floors:

- Individual pre-diluted kefir dosing containers will no longer be sent to ICU. Plain and flavored kefir will be stocked in the Patient frig. Call 3663 if you need more. Plain Kefir for enteral administration. Flavored Kefir for oral administration.
- Kefir stickers will be put on tube feeding bottles that come up in am. This will serve as a reminder to nurses that kefir has been ordered.

Directions for ICU:

- Kefir for oral swab bid if on vent with hi/lo suction (not if trach): dip sponge into kefir and swab mouth about 30-60 minutes after chlorhexidine/oral care twice daily.
- Kefir for oral intake: about 60 ml (2 oz) fruit flavored kefir once or twice a day or as ordered.
- Kefir for tube feeding: mix 45 ml (1.5 oz) plain kefir plus about 45 ml water together, syringe into feeding tube. flush with water before and after administration. Usually twice daily.

Oral Probiotic Swabs for prevention of ventilator associated events.

- Order "Kefir for TF bid" add comment “swabs only” if don’t want enteral administration
- Order "Kefir for mouth swabs" this is a nursing order and does not go to the kitchen.
- Must order both. Do not order mouth swabs alone or kefir will not be delivered from the kitchen.
- Delivery to both the oral cavity and enterally maximizes benefits for prevention of VAE/VAP.
- Kefir for oral swab bid if on vent with hi/lo suction (not if trach): dip sponge into kefir and swab mouth about 30-60 minutes after chlorhexidine/oral care
- Consider Culturelle® if Nancy’s kefir is contraindicated or patient on fluid restrictions. 1 capsule in surgilube swabbed into oral cavity and 1 capsule in ~30 ml water via feeding tube, do twice daily after oral care.

Discharge instructions:

- Review patient instructions for continuing Nancy’s kefir after discharge on printed after visit summary.

Cautions:

- Do not add directly into Tube Feeding Formula or bag
- Use plain kefir, not flavored kefir, if administering kefir yogurt through a feeding tube. Flavored kefir has pieces of fruit that could clog the feeding tube.
- Refrigerate remaining portion of individual dosing container. Discard after 24 hours.
- Keep unused individual doses refrigerated until time of administration, allow to warm to room temperature if concerned about cramping.
• Cartons of Kefir should be discarded after the “Enjoy by” date printed on carton (floor stock item)
• Separating probiotics from oral antibiotics by ~2 hours may help maximize probiotic survival
How to guide to implement a Hospital Based Probiotic Protocol for prevention of *C. difficile* at your hospital

Where to start? Fill in the blanks below for your hospital and create short PowerPoint.

**Slide 1: The problem of *Clostridium Difficile* Infection (CDI)**

According to the CDC:

- Patients on antibiotics are 7-10 times more likely to get CDI
- CDI can occur up to a month after taking an antibiotic
- CDI comes back in 1 in 5 patients
- 1 in 11 people 65 and older die within a month of being diagnosed with *C. difficile* infection


**Slide 2: The problem of *Clostridium Difficile* Infection (CDI)**

- Hospital mortality is higher for patients with *C. difficile*:
  - 9.1% vs. 1.9%. (Lucado et al 2012)
- Hospital costs are $15,000 higher for patients with *C. difficile*:
  - $24,000 vs. $9,000 per hospital stay (Lucado et al 2012)

**Slide 3: Our problem:**

- Our rate of hospital acquired *C. difficile* rate is ___ cases per 10,000 patient days. (CDC’s National Healthcare Safety Network [http://www.cdc.gov/nhsn/](http://www.cdc.gov/nhsn/))
- Our Standardized Infection Ratio (SIR) is ____ This is worse than national rate/worse than expected. (Hospital Compare CMS website [https://www.medicare.gov/hospitalcompare/search.html](https://www.medicare.gov/hospitalcompare/search.html))

**Slide 4: Our solution:**

- About ____ cases a year, about half, can be prevented with full implementation of probiotic protocol with the right type of probiotic
- Results in cost savings of $______ a year for our patients and hospital. [Multiply $15,000 per case avoided per hospital stay.]
- Hospital ratings and reimbursement are tied to our outcomes. We can make a difference.

**Slide 5: A Hospital Based Probiotic protocol is simple, safe and effective and improves care, costs, and outcomes for our patients.**

The truth about probiotics and *C. difficile*:

- Some types of probiotics have no effect at all on *C. difficile*
- Some probiotics only work when you feed them (3-10 g prebiotics) which they use to acidify the colon pH<6 and inhibit *C. difficile* growth
- Some probiotics reduce the risk of *C. difficile* ~40-80% in right dose:
  - DanActive® 3.5 ounce bottle twice a day, 65% lower risk
  - Nancy’s Kefir 2 ounces once or twice a day, 42-57% lower risk
  - Nancy’s yogurt 4 ounces once or twice a day, 44% to 64% lower risk
  - Culturelle® 1 capsule once or twice a day, ~40% less risk
  - Florostor® 250 mg capsule 1 to 2 caps twice a day, ~60% less risk

Start probiotics within 2 days of starting antibiotics, take 2 hours apart from antibiotic, continue probiotics at least 7 days after complete course of antibiotics. Contraindications: ANC<500, severely immunosuppressed, milk allergy to food sourced probiotics.

**Slide 6: Key References:**


Hospital Compare CMS website [https://www.medicare.gov/hospitalcompare/search.html](https://www.medicare.gov/hospitalcompare/search.html)


Nancy’s Yogurt: Legacy Health system 2013 Hospital Compare SIRs for Legacy hospitals in Portland, Oregon who use Nancy’s yogurt probiotic protocol.

Nancy’s Kefir: Good Samaritan Regional Medical Center, Corvallis, Oregon, 2012-2015 Hospital Compare and CDC National Healthcare Safety Network. GSRMC uses Nancy’s Kefir Probiotic protocol, rate <4.0/10,000 (p<0.03 vs. CDC expected rate) satthomas@samhealth.org
**Which to choose:** If you can’t get Nancy’s Kefir in your area use DanActive® instead. It is available nationwide and has comparative effectiveness for prevention of C. difficile (65% lower, Hickson et al) and comes in easy single dose 3.5 oz bottles that should be taken twice a day. The cost is typically about twice as much as Nancy’s Kefir. About $20 per patient for complete protocol. If pt is allergic to dairy use Florostor® or dairy free Culturelle® These other probiotic options typically cost 2 to 5 times more than Nancy’s Kefir. Nancy’s Kefir and Nancy’s yogurt are from an Oregon company [www.nancysyogurt.com](http://www.nancysyogurt.com). It costs $0.18 to $0.88 per day based on product choice (plain vs. flavored kefir), dosing amount for >=10 billion CFU (45 ml plain kefir, 60 ml flavored kefir, 120 ml yogurt), dosing frequency (qd minimum effective dose, bid recommended) and institutional and retail price range ($3 to $7 per 32 ounce container).

**Cost impact:** It is true that the cost hits the food and nutrition dept while the cost benefits accrue to the pt and the hospital, but at only $4,000 to $5,000 a year for us (188 bed hospital), is very low price to pay to earn that kind of positive impact and good will as you help solve a very tough and costly problem. You can also arrange to bill the hospital for the cost since it is easy for most vendors to run a report on how much of an item you purchased during a set date window and bill the hospital on a monthly, quarterly or annual basis.

**Cost savings:** Nancy’s kefir had a ROI of $31:1 on average at GSRMC. 2012 to 2015 we have prevented over 39 cases of hospital acquired C. difficile, prevent 3 hospital deaths, and had a net savings of over half a million dollars. GSRMC now has hospital acquired C. difficile rate of <4.0 cases per 10,000 patient days, p<0.03 vs. CDC expected for our hospital. We spend $4,000 to $6,000 annually on Nancy’s Kefir for our 188 bed level II trauma center and regional medical center and teaching hospital with roughly 40,000 annual patient days and around 10,000 annual patient discharges. Making flavored kefir a floor stock item freely available for nursing staff to administer per protocol when indicated and not contraindicated led to significant improvement 42-57% lower vs. orders only (non-significant 15 to 16% lower). Note: Lifeway Kefir is not as good as Nancy’s for C.diff (lacks certain probiotics) plus actual costs at least double because lower probiotic level means it takes 2-3 cups a day to get >=20 billion CFU vs. ½ cup for Nancy’s kefir. Why brand names? Must name specific brands because that’s the specific evidence. Generic substitutions may be useless.

**Negotiating change/push back:** Probiotics are therapeutic class of hundreds—some as different as dogs and turtles! It is a common mistake to lump all probiotics together for analysis like they are one thing. You can expect push back from doctors who read “Up-to-date” or other “evidence based” summaries which have treated probiotics like one therapeutic agent instead of like a therapeutic class of hundreds. “Only doctors should order”? Our experience was that being too restrictive with implementation (orders only) resulted in less implementation and less beneficial outcomes than when it was made more freely available as a floor stock/nurse delivery as well (16% vs 57% lower rates). However enteral (tube feeding) delivery should always be orders only since these pts are more likely to be critically ill and have some relative contraindications that need to be considered. Once you have a draft protocol, drum up administrative and clinical support, start with infection prevention and hospitalists. Use the 3 key articles to discuss (JAMA, Ann Intern Med, Cochrane). Be sure to emphasize the risk/benefits and that while probiotics are still a new and emerging science for some other conditions, this (AAD/C.diff) is an area where the evidence is good, the risk is low, and the risk of not acting is high, 1 out of 11 pts over 65 will die within 30 days of contracting c.diff infection (CDC). Leaning on that risk/benefit angle is very productive when discussing with MDs. Admin will be interested in that as well as the financial cost saving aspect.

For more information email sathomas@samhealth.org or sara.thomas@sodexo.com